

School of Physiotherapy and Exercise Science

**Evaluation of Predictors for Persistent Pain Post-total Knee
Replacement**

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Doctor of Clinical Physiotherapy
of
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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

A handwritten signature in black ink, consisting of a large loop followed by a horizontal stroke and a small flourish.

Kwok Chee Philip Cheong

21 December 2017

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Abstract

Persistent pain post-total knee replacement (TKR) surgery may be due to either a pre-existing pain condition or 'new' pain after TKR. This may be the reason why the prevalence of persistent pain post-TKR surgery has been shown to range from 13% to 44%. Even though multiple risk factors for developing persistent pain post-TKR surgery have been considered, there is currently no standardised method of accurately predicting who will develop this condition. A series of three studies were conducted to investigate the issue of persistent pain post-total knee replacement.

The first study evaluated the differences in health status, clinical presentation (pain quality, neuropathic pain symptoms) and quantitative sensory testing responses (heat, cold, pressure) between 2 groups of patients at least one year after their TKR surgery. The patients were divided into "no pain" and "moderate to severe pain" groups based on the Knee Society Score recorded independently by Joint Replacement Assessment Clinic staff one year post surgery. The results of the first study demonstrated that the "moderate to severe pain" group reported significantly higher levels of neuropathic-type pain and exhibited widespread mechanical and cold hyperalgesia as compared to the "no pain" group.

The second study evaluated whether the response of healthy participants to two different sustained cold stimuli remained stable between 2 separate test occasions. The results of the second study demonstrated the excellent reliability of the two alternative ways of testing cold response, and the positive correlations between the standard way of testing for cold pain response and the two alternative cold tests. Due to its relative ease of use, the sustained cold response test was utilised as a quantitative sensory test in the final study.

The third study evaluated the predictive value of pre- and post-operative psychological (depression, pain catastrophising), clinical (pain quality, neuropathic pain symptoms, sleep disturbances), quantitative sensory testing (heat, cold, pressure) and intra-operative data (surgical approach, anaesthesia) in identifying the likelihood of developing persistent pain post-TKR.

Multiple linear regression was used to determine the predictive value of a range of key measures (quantitative sensory testing, PainDETECT score, functional level, quality of life and psychological distress) in determining persistent pain post-TKR. In addition, receiver operating characteristic curve analysis was used to determine the sensitivity and specificity of any measures identified in the multiple linear regression model in terms of their capacity to identify those who do or do not have persistent pain post-surgery. The results of the third study demonstrated that there were significant pre-operative differences in TKR patients who reported higher pain levels at 3 and 6 months after surgery. Further analysis revealed that there were several pre-operative measures which were found to be predictive of higher pain levels and poor outcome at 3 and 6 months respectively. Several of these measures are of interest since they are potentially modifiable and can be grouped into 4 risk factor categories: psychological distress, neuropathic-type pain, impaired physical function and reduced sleep quality. The findings of this clinical doctorate research provide the basis for the development of a standardised protocol for predicting the type of patients who are likely to develop persistent post-operative pain prior to undertaking total knee replacement. This creates the opportunity to develop pre-surgical preparation programmes aimed at reducing the individual risk of developing significant post-surgical pain.

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Chapter 1

Literature Review

1.1. Introduction

The purpose of this study was to establish the basis for a standardised protocol for pre-operative identification of patients who will develop persistent post-operative pain following total knee replacement surgery. This literature review chapter will explore:

- The current understanding of osteoarthritis (OA)
- The complexity of OA pain
- The different factors that influence OA pain
- Current management of OA pain
- Persistent pain post-total knee replacement

1.2. Background

1.2.1. Osteoarthritis

1.2.1.1. Definition of Osteoarthritis

The Osteoarthritis Research Society International (OARSI) defines OA as “a disorder involving movable joints characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injury that activates maladaptive repair responses including pro-inflammatory pathways of innate immunity. The disease manifests first as a molecular derangement (abnormal joint tissue metabolism) followed by anatomic, and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation and loss of normal joint function), that can culminate in illness.” (Kraus et al., 2015).

1.2.1.2. Prevalence

The 2011-2012 Australian Health Survey showed that 14.8% (around 3.3 million) of Australians suffer from arthritis, with a higher prevalence in females (17.7%) compared to males (11.8%) (Australian Bureau of Statistics [ABS], 2012). 55.9% of Australians who had arthritis reported that they suffered from OA (Australian Institute of Health and Welfare [AIHW], 2011).

For the financial year 2008-2009 in Australia, \$1637 million was spent on the care of osteoarthritis sufferers (AIHW, 2014).

1.2.1.3. OA pain

Nociception

OA is characterized by articular cartilage degeneration, the subsequent breakdown of the joint surface and hypertrophic bone changes (Martel-Pelletier, 2004).

Articular cartilage does not have any innervation, blood and lymphatic vessels, therefore articular cartilage degeneration is not considered to be the cause of nociceptive pain in OA (Fox et al., 2009). However, the joint surfaces (periosteum and subchondral bone) are richly innervated and together with the surrounding structures (i.e. synovial membrane, joint capsule, periarticular ligaments, bone) form the sources of nociceptive pain in OA (Hunter et al., 2008).

Pain presentation

The presentation of pain in knee OA varies greatly, from localised activity-related pain to referred pain and even widespread pain at sites distant from the knee (Arendt-Nielsen et al., 2010; Bajaj et al., 2001; Graven-Nielsen et al., 2012; Kidd, 2006). Pain intensity levels also vary widely, without necessarily being linked to extent of OA changes. Several studies into knee OA have found that there is a poor correlation between degree of OA damage on imaging and self-reported pain intensity (Bedson & Croft, 2008; Creamer et al., 1999; Davis et al., 1992), although a relationship between the development of bone marrow lesions in the underlying bone and the magnitude of knee pain has been demonstrated (Felson et al., 2001).

Due to this variability in pain presentation, independent of physical signs of OA, it has been hypothesized that both peripheral and central pain processes may be active to varying degrees in patients with knee OA (Arendt-Nielsen et al., 2010).

Pain processes

Peripheral sensitisation is likely to be driven by inflammation of the damaged structures in the OA joint, whereas central sensitisation may be driven by the continuous intense nociceptive input from the OA joint (Arendt-Nielsen et al., 2010). In central sensitisation there is a change in the properties of the central nervous system neurons, such that pain may no longer be coupled to the presence or intensity of noxious peripheral stimuli (Latremoliere & Woolf, 2009). Gwilym et al. (2009) used quantitative sensory testing and functional brain imaging to investigate the presence of central sensitization in hip OA patients with referred pain. The investigators reported that functional brain imaging demonstrated significant activation of the periaqueductal grey (PAG) area in the hip OA patients as compared to healthy controls (Gwilym et al., 2009). Based on the scores for the PainDETECT questionnaire (a validated self-report screening tool that identifies features of neuropathic pain), the hip OA group was split into a high and low PainDETECT score group. During punctate stimulation of the referred pain area in the hip OA patients, the high PainDETECT group showed significantly greater PAG activation as compared to the low PainDETECT group (Gwilym et al., 2009). The results of this study demonstrate the involvement of the PAG in neuroplastic changes associated with central sensitization in a sample of hip OA patients (Gwilym et al., 2009).

Neuroplastic changes

A study investigating brain gray matter volume changes in OA pain found that patients with painful hip OA exhibited significantly decreased thalamic gray matter volume as compared to healthy controls (Gwilym et al., 2010). Following total hip replacement (THR) surgery, the investigators found that there was a significant increase in the thalamic gray matter volume in the patients compared to pre-surgery. This increase in the patients' post-surgery thalamic gray matter volume showed no significant difference when compared against the healthy controls (Gwilym et al., 2010). Rodriguez-Raecke et al. (2009) also investigated brain gray matter volume changes in patients with chronic hip OA pain. The investigators reported that pre-operative brain imaging revealed that the hip OA patients had significantly

decreased brain gray matter in the anterior cingulate cortex (ACC), right insular cortex and operculum, dorsolateral prefrontal cortex (DLPFC), amygdala and brainstem as compared to the control group (Rodriguez-Raecke et al., 2009). A subgroup of the hip OA patients was followed through to 4 months post-THR surgery, where brain imaging revealed a significant increase in brain gray matter in the ACC, right insular cortex, DLPFC, amygdala and the brainstem (Rodriguez-Raecke et al., 2009). The results of the 2 above studies suggest that chronic OA pain leads to changes in brain morphology which is reversible following removal of the source of nociception.

A recent brain imaging study on pain sensitization in patients with knee OA reported that pain sensitization secondary to knee OA was common, and that it was associated with neuroplastic changes extending beyond the normal pain-processing brain regions, with increased activity in the posterior sensory, non-nociceptive brain areas (Pujol et al., 2017).

Functional brain imaging studies in patients with OA have demonstrated an important role of the affective and motivational aspects of pain (Neogi, 2013). Parks et al. (2011) investigated brain activity in chronic knee OA and reported that in spontaneous OA pain the brain regions activated were the medial prefrontal cortex and limbic areas. The prefrontal and limbic areas are brain structures that are implicated in emotional processing and conditioning of fear, hence this suggests that spontaneous OA pain has a strong emotional component (Parks et al., 2011). The spontaneous knee OA pain-related brain activation pattern shows close resemblance to the spontaneous pain-related brain activation patterns for chronic back pain and post-herpetic neuralgia (Parks et al., 2011). In another study, positron emission tomography (PET) of the brain was performed on knee OA patients during 3 different pain states: arthritic knee pain, experimental knee pain and pain-free (Kulkarni et al., 2007). The results of the study revealed that during PET scans of the brain in the arthritic pain state there was significantly greater activation of the cingulate cortex, thalamus and amygdala (Kulkarni et al., 2007). These brain structures are implicated in fear and emotional processing as well as aversive conditioning, also indicating that there is a strong emotional aspect in arthritic pain (Kulkarni et al., 2007).

Neuropathic pain

The presence of neuropathic pain symptoms in OA has been shown in several types of studies. Basic science studies of OA pain have identified a neuropathic pain component in animal models of OA pain (Harvey & Dickenson, 2009; Im et al., 2010; Ivanavicius et al., 2007).

Pharmacological studies on OA pain in humans revealed that some neuropathic pain medications (e.g. pregabalin, duloxetine, tanezumab) are effective in the control of OA pain.

Pregabalin is an anticonvulsant that has analgesic and anxiolytic properties, and has been shown to be effective in the treatment of neuropathic pain (Freynhagen et al., 2005; Rosenstock et al., 2004; Sabatowski et al., 2004). Wright et al. (2017) investigated the use of pregabalin in individuals with knee OA who presented with neuropathic pain, and reported that the intervention group demonstrated significant reductions in pain levels, neuropathic pain features and tenderness in the affected knee as compared to a control group taking paracetamol.

Duloxetine is a serotonin-norepinephrine reuptake inhibitor and has been proven to be effective in the treatment of polyneuropathies (Baron et al., 2010). The efficacy of duloxetine in the treatment of OA pain has been investigated in several pharmacological studies. The results of these studies have shown that duloxetine significantly reduces pain intensity and improves function in OA patients (Chappell et al., 2011; Chappell et al., 2009; Sullivan et al., 2009; Wise, 2010).

Nerve growth factor (NGF) has been implicated as a major mediator of neuropathic pain, and suppression of NGF activity have been shown to lead to the reduction of the hyperalgesic state commonly associated with neuropathic pain (Watson et al., 2008). Tanezumab is a drug that acts by inhibiting the binding of NGF to its receptors, and when used in knee OA patients it has resulted in significant reductions in pain, stiffness and limitations in functional capabilities (Brown et al., 2012; Lane et al., 2010). Cedraschi et al. (2013), Hawker et al. (2008) and Hochman et al. (2010) evaluated the pain quality of focus group participants with OA pain and found that a proportion of participants used characteristic neuropathic pain descriptors when describing their pain. Using patient report questionnaires,

several studies have demonstrated the presence of neuropathic pain symptoms in people with OA pain (Hochman et al., 2013; Hochman et al., 2011; Moreton et al., 2015; Moss et al., 2017; Ohtori et al., 2012; Oteo-Álvarez et al., 2015; Shigemura et al., 2011; Wright et al., 2017).

Psychosocial factors

A systematic review on the influences of psychosocial factors in OA pain reported that “pain catastrophizing and self-efficacy show consistent links to pain and pain-related outcomes” (Somers et al., 2009).

Pain catastrophizing is described as an excessive negative focus on pain, magnification of the pain sensation and a sense of helplessness in the individual’s capability to deal with the pain (Sullivan et al., 2001). Scott et al. (2016) conducted a longitudinal study which investigated the effects of psychological distress in a cohort of patients with chronic musculoskeletal pain. The investigators reported that depression and pain catastrophizing were identified as strong predictors of increased pain. A prospective study on the predictive value of psychological factors in determining poor outcomes post-TKR revealed that pre-operative pain catastrophizing was a unique predictor of pain at 6-week follow-up (Sullivan et al., 2009). Pain catastrophizing has also been reported as a significant predictor of increased sensitivity to physical activities in a cohort of individuals with knee OA (Wideman et al., 2014). Keefe et al. (2000) investigated the role of catastrophizing in the relationship of gender to pain in OA patients, and found that women had significantly higher levels of pain and catastrophizing as compared to men. Using mediational analyses, the investigators also reported that pain catastrophizing had a significant positive association ($\chi^2=5.70$, $P=0.46$; NFI=0.97; CFI=1.00) with pain-related outcomes (pain levels and physical disability) regardless of gender (Keefe et al., 2000). Self-efficacy has been defined as an individual’s belief in his or her capability to engage in a course of action to achieve a desired outcome (e.g. control of their pain) (Bandura, 1978). A study of overweight/obese individuals with knee OA found that pain catastrophizing led to higher levels of pain and disability through lowered self-efficacy, meaning that high self-efficacy will lead to lesser pain and disability (Shelby et al., 2008). OA patients who had

higher self-efficacy in communicating pain to their partners, had significantly lower levels of catastrophizing, caregiver strain (in their partners), pain, physical and psychological disability (Porter et al., 2008). A randomized controlled study on the effects of spouse-assisted coping skills training and exercise training in patients with chronic OA knee pain demonstrated that the combined coping skills and exercise training group reported significant improvements in self-efficacy and reductions in psychological disability (Keefe et al., 2004).

Creameans-Smith et al. (2003) examined agreement between OA patients and two role partners (spouses and rheumatologists) on the patient's pain severity and well-being. Patients who had dyadic agreement with their spouses had consistently better psychological well-being, whereas patients had better psychological well-being when their rheumatologist underestimated their pain severity (Creameans-Smith et al., 2003).

Apart from the psychosocial factors listed above, educational level has also been identified as a significant factor for self-reported pain and physical function in OA; with higher education levels reflecting lower pain levels (Cimmino et al., 2005; Juhakoski et al., 2008; Thumboo et al., 2002).

Sleep disturbance

Sleep disturbance is a common problem, with up to 70% of knee OA sufferers having poor sleep quality (Hawker et al., 2010). In normal and healthy subjects, sleep deprivation has been shown to cause thermal hyperalgesia, and increased sensitivity to mechanical pain stimuli (Schuh-Hofer et al., 2013). Another experimental sleep model study in healthy participants reported that chronic exposure to insufficient sleep reduced the body's ability to habituate to experimental cold pain, and the authors concluded that chronic insufficient sleep could potentially increase an individual's vulnerability to chronic pain (Simpson et al., 2017). In knee OA sufferers, greater sleep disturbance has been correlated to more arthritic joints ($r=0.15$, $P<0.01$), increased knee pain ($r=0.13$, $P<0.01$) and poorer physical functioning (FAST Functional Performance Inventory: $r=0.25$, $P<0.001$; 6-minute walk test: $r=-0.1$ $P<0.01$) (Wilcox et al., 2000).

Summary

In summary, there are multiple mechanisms (nociceptive pain, neuroplastic pain and neuropathic pain), pain processes (peripheral sensitisation, central sensitisation), sleep disturbance and psychological/social factors that contribute to the generation of OA pain. To further complicate the nature of OA pain: the mechanisms, pain processes and factors that mediate OA pain vary substantially among individuals (Kidd, 2006; Suokas et al., 2012).

1.2.1.4. Assessment of widespread sensitisation and neuropathic pain

In the last 10-15 years, there has been an increased emphasis on using a combination of quantitative sensory testing and neuropathic pain questionnaires as a way of assessing both widespread sensitisation and neuropathic pain (Arendt-Nielsen & Yarnitsky, 2009; Backonja et al., 2013; Bennett et al., 2007; Bennett et al., 2005; Cruz-Almeida & Fillingim, 2014; Felix & Widerström-Noga, 2009; Freynhagen & Baron, 2006; Gwilym et al., 2011; Hochman et al., 2013; Hochman et al., 2011; Jespersen et al., 2010; Krumova, 2010; Ohtori et al., 2012; Pavlaković & Petzke, 2010; Rommel et al., 2001; Shigemura et al., 2011; Shy et al., 2003; Uddin & MacDermid, 2016; Walk et al., 2009; Wylde et al., 2012).

1.2.1.4.1. Quantitative sensory testing

Quantitative sensory testing (QST) has been widely used to explore local and widespread pain in OA. QST been defined as “the determination of thresholds or stimulus response curves for sensory processing under normal and pathophysiological conditions” (Arendt-Nielsen & Yarnitsky, 2009). QST uses a psychophysical testing approach to quantify somatosensory function in individuals (Backonja et al., 2013). This psychophysical approach means that QST is semi-subjective as it assesses an individual’s subjective responses to a controlled stimulus (Uddin & MacDermid, 2016). QST assesses the functional status of the entire somatosensory system, and threshold detection testing can be used to quantify / monitor the presence of both negative (e.g. hypoalgesia) and positive (e.g. hyperalgesia) sensory

phenomena (Backonja et al., 2013; Uddin & MacDermid, 2016). Threshold determination is indicative of basal sensitivity (of the somatosensory system), and is easily defined and identifiable (Arendt-Nielsen & Yarnitsky, 2009; Uddin & MacDermid, 2016). Table 1.1 lists some QST stimuli and the somatosensory channels assessed.

Table 1.1: QST Stimuli and somatosensory channels

Stimulus	Sensation Elicited	Peripheral Sensory Channel	Central Pathway
Blunt Pressure	Sharp Pain	A δ , C	Spinothalamic
Vibration	Vibration	A β	Lemniscal
Heat Detection	Heat	C	Spinothalamic
Heat Pain	Painful Heat	A δ , C	Spinothalamic
Cold Detection	Cold	A δ , C	Spinothalamic
Cold Pain	Painful Cold	A δ , C	Spinothalamic

Based on Backonja et al. (2013) and Uddin and MacDermid (2016)

There are 2 general testing algorithms for QST, the method of limits and the method of levels (Backonja et al., 2013; Shy et al., 2003; Uddin & MacDermid, 2016). In the method of limits, a stimulus of increasing or decreasing intensity is applied to the test site and the subject is required to press a control switch/button when they perceive or feel a stimulus as being present or being painful (Shy et al., 2003; Uddin & MacDermid, 2016). In the method of levels, a series of stimuli of predetermined intensity are applied to the test site and the subject must choose whether the stimulus is felt or not, or whether the stimulus is painful or not (Shy et al., 2003; Uddin & MacDermid, 2016). Backonja et al. (2013) stated that “the method of limits is less time consuming and therefore more commonly used for both clinical and research”.

Due to the complex pathophysiology of OA pain, QST is a useful approach that can be used to evaluate mechanism-based phenotyping of OA pain (Cruz-Almeida & Fillingim, 2014; Suokas et al., 2012; Wylde, et al., 2011).

1.2.1.4.2. Widespread sensitisation

Due to inflammation and tissue damage, changes in the processing (increased responsiveness) of peripheral and central nociceptor pathways can lead to pain sensitisation in OA (Neogi, 2013).

A number of studies have shown the presence of sensitisation in knee OA. Arendt-Nielsen et al. (2010) reported that knee OA patients with high levels of pain exhibited widespread pressure pain sensitisation as compared to healthy controls.

Wright et al. (2017) investigated the extent of multi-modality (thermal and pressure) hyperalgesia experienced by patients with knee OA and found that the knee OA group exhibited widespread cold hyperalgesia as compared to healthy controls. 43.75% of the knee OA group were classified as cold hyperalgesic and this sub-group exhibited widespread multi-modality sensitisation as compared to the remaining cohort of OA sufferers (Wright et al., 2017).

A study investigating sensitization in patients after revision TKR found that patients with chronic pain after revision TKR had significantly more pain sites, lower cuff pressure pain thresholds and tolerance at the calf, as well as lower pressure pain thresholds at the index knee, tibialis anterior muscle and forearm (Skou et al., 2013).

Wylde et al. (2013) reported that TKR patients with lower pre-operative pressure pain thresholds at their forearm had higher pain levels in their operated knee at 1 year post-TKR surgery. It was not reported whether this group of TKR patients had higher levels of pain pre-operatively.

Similarly, Graven-Nielsen et al. (2012) also found that knee OA patients exhibited widespread pressure pain sensitivity as compared to healthy controls. Normalization of the pressure pain thresholds occurred following TKR surgery for this group of patients (Graven-Nielsen et al., 2012). It must be noted that the patients in the above study also reported significant reductions in their pain following TKR.

Petersen et al. (2016) investigated the relationship between pre-operative pain mechanisms in knee OA patients and pain levels at 1 year post-TKR

surgery. The investigators reported that the presence of pre-operative widespread pain sensitisation was associated with higher pain levels at 1 year post-TKR.

Based on the current evidence, there is an association between widespread pain sensitivity and OA pain.

1.2.1.4.3. Neuropathic pain

Neuropathic pain is defined by the International Association for the Study of Pain (IASP) as “pain caused by a lesion or disease of the somatosensory system” (<http://www.iasp-pain.org/Taxonomy#Neuropathicpain>)(Jensen et al., 2011).

1.2.1.4.3.1. Identification of neuropathic pain – use of PainDETECT questionnaire

Patients with neuropathic pain exhibit both negative and positive sensory signs and symptoms (Baron et al., 2010). Persistent or paroxysmal pain are also hallmarks of neuropathic pain syndromes (Woolf & Mannion, 1999). Diagnosis of neuropathic pain is based on the patient’s self-reported pain characteristics, the presence of somatosensory abnormalities and laboratory studies (Dworkin et al., 2003; Hochman et al., 2011; Jensen et al., 2001; Treede et al., 2008).

Pain characteristics can be measured by self-report pain questionnaires such as the PainDETECT questionnaire (Appendix 1). The PainDETECT questionnaire is a reliable screening tool with good internal consistency (Cronbach’s Alpha: 0.83), high sensitivity (85%), specificity (80%) and positive predictive accuracy (83%) of a neuropathic pain component being present in chronic low back pain sufferers (Freynhagen & Baron, 2006). It has also been used in a number of studies looking at the presence of neuropathic pain features in other musculoskeletal conditions including osteoarthritis (Gwilym et al., 2011; Hochman et al., 2013; Hochman et al., 2011; Jespersen et al., 2010; Ohtori et al., 2012; Shigemura et al., 2011). Other neuropathic pain questionnaires (e.g. S-LANSS, DN4) have also been used to evaluate features of neuropathic pain in the OA population (Moreton et al., 2015; Oteo-Álvaro et al., 2015).

1.2.1.4.3.2. Prevalence of neuropathic pain in OA

A number of studies using the PainDETECT questionnaire found that the prevalence of neuropathic-type pain symptoms in OA ranges from 18.5% to 34% (Hochman et al., 2011; Moss et al., 2017; Ohtori et al., 2012; Shigemura et al., 2011; Valdes et al., 2014). Shigemura et al. (2011) investigated the relationship between neuropathic pain and hip OA pain, and found that 18.5% of their study sample had features of neuropathic pain. In another study, investigators using the PainDETECT questionnaire found that 20.6% of knee OA patients reported components of neuropathic pain (Ohtori et al., 2012). Using a modified version of the PainDETECT questionnaire, Hochman et al. (2011) found that 28% of individuals in a community cohort of symptomatic knee OA sufferers had symptoms of neuropathic pain. Valdes et al. (2014) reported that up to 34% of patients with severe painful knee OA had PainDETECT questionnaire scores corresponding to having possible neuropathic pain. They also found that a history of past knee surgery was strongly associated with possible neuropathic pain (Valdes et al., 2014).

1.2.1.4.3.3. Prevalence of neuropathic pain post-TKR

The prevalence of neuropathic pain post-TKR ranges from 5.2% to 41% (Albayrak et al., 2016; Buvanendran et al., 2010; Fuzier et al., 2015; Harden et al., 2003; Haroutiunian et al., 2013). Albayrak et al. (2016) investigated risk factors for persistent pain following TKR and found that patients with persistent pain post-TKR scored higher in the PainDETECT questionnaire as compared to TKR patients without persistent pain. The investigators reported the prevalence of neuropathic pain after TKR (mean time of 22.8 ± 12.3 months) to be 15.3%.

A randomized controlled trial of perioperative oral pregabalin before TKR reported that in their control group, the incidence of neuropathic pain was 8.7% at 3 months and 5.2% at 6 months post-TKR (Buvanendran et al., 2010).

Fuzier et al. (2015) investigated the incidence of persistent pain 3 months following orthopaedic surgery, their results showed that the prevalence of neuropathic pain at 3 months after orthopaedic surgery was 20%. Closer analysis of the results revealed that the prevalence of neuropathic pain at 3 months after TKR was 41%.

A prospective study on the predictive utility of emotional distress and pain intensity on the occurrence of complex regional pain syndrome reported that the prevalence of neuropathic pain was 21% at 1 month, 13% at 3 months and 12.7% at 6 months post-TKR (Harden et al., 2003).

A systematic review reported that the prevalence of probable/definitive neuropathic pain in total knee arthroplasty/total hip arthroplasty patients with persistent post-surgical pain is about 5.7% (Haroutiunian et al., 2013).

1.2.1.4.3.4. Cold hyperalgesia as an indicator of neuropathic pain

Cold hyperalgesia is a clinical feature commonly exhibited in individuals with neuropathic pain (Baron et al., 2010), and has been documented in the literature to be a prognostic factor for the development of chronic pain and disability in some musculoskeletal conditions such as whiplash associated disorder (Goldsmith et al., 2012; Maxwell & Sterling, 2013) and lateral epicondylalgia (Coombes et al., 2012). It has been proposed that the presence of widespread cold hyperalgesia alongside self-reported neuropathic pain may particularly reflect widespread central sensitisation in OA (Gwilym et al., 2009; Hochman et al., 2013).

1.2.1.4.3.5. Cold hyperalgesia in OA – Evidence

Several studies have reported the presence of cold hyperalgesia in knee OA. Wright et al. (2017) aimed to establish the extent of multi-modality hyperalgesia in a cohort of knee OA patients. The investigators reported that the knee OA patients had widespread cold hyperalgesia as compared to controls, they also identified a sub-group of patients with knee OA with high global cold pain threshold that exhibited multi-modality hyperalgesia as compared to the rest of the OA group. King et al. (2013) investigated experimental pain sensitivity in symptomatic knee OA and reported that individuals with higher pain levels were significantly more sensitive to cold

stimuli as compared to controls and the low symptom knee OA group. Another study investigated the presence of widespread mechanical and thermal hyperalgesia in knee OA patients and reported that the knee OA group demonstrated significantly increased widespread sensitivity to both pressure and cold stimuli as compared to controls (Moss et al., 2016).

1.2.1.4.3.6. Cold hyperalgesia as a predictor of persistent pain

In whiplash associated disorders, the presence of cold hyperalgesia has been demonstrated to be a significant predictor of poor outcome at short and long term follow-up (Goldsmith et al., 2012; Sterling et al., 2012; Sterling et al., 2006; Sterling et al., 2003; Sterling et al., 2005). Sterling et al. (2011) investigated the developmental trajectories for neck disability and post-traumatic stress disorder (PTSD) following whiplash injury. The investigators reported that the same baseline factors of cold hyperalgesia, high initial pain levels and older age predicted both chronic/severe neck disability and chronic moderate/severe PTSD trajectory.

Coombes et al. (2012) investigated sensory, motor and psychological factors in patients with varying severity of lateral epicondylalgia (LE), and reported that patients with severe LE had bilateral cold hyperalgesia as compared to controls. Based on the findings of the above study, the same investigators conducted a prognostic study of physical and psychological factors in LE and reported that cold hyperalgesia was the only consistent predictor of poor prognosis in LE (Coombes et al., 2015).

Currently, cold hyperalgesia has not been extensively investigated as a predictor of persistent pain post-TKR.

1.2.1.4.3.7. Clinical measurement of cold hyperalgesia

Assessment of cold hyperalgesia is relatively complex. Metal rollers, test tubes filled with ice/chilled water, ice or coolants and simple ice cubes are some of the methods used to assess cold hyperalgesia in the clinical setting (Baron et al., 2010; Maxwell & Sterling, 2013; Uddin & MacDermid, 2016; Walk et al., 2009). These methods are imprecise and prone to errors, as there is no way of controlling the temperature of the cold stimulus and the patient response.

Testing of cold hyperalgesia in the research setting is usually performed with a computer-controlled peltier thermode (Cruz-Almeida & Fillingim, 2014; Geber et al., 2011; Hagander et al., 2000; Heldestad et al., 2010; Krumova, 2010; Shy et al., 2003; Walk et al., 2009). These devices can generate precise repeatable stimuli but their complexity and the high cost of these devices are major barriers to their widespread use in the clinical setting. There is potential value in developing new clinical methods to assess cold hyperalgesia.

1.2.1.5. Management of OA pain

There are multiple guidelines available on the management of knee OA pain (Hochberg et al., 2012; Larmer et al., 2014; McAlindon et al., 2014; Nelson et al., 2014). The consensus on the management of knee OA pain is that it is based on symptom severity, and the treatment options available are classified under non-pharmacological, pharmacological, complementary and lastly, surgical interventions. Optimal conservative management of knee OA pain must be individualized and requires a combination of both non-pharmacological and pharmacological interventions (Taruc-Uy & Lynch, 2013; Zhang et al., 2008).

The recent Osteoarthritis Research Society International (OARSI) guidelines for the non-surgical management of knee OA recommended treatments based on 4 clinical knee OA sub-phenotypes (McAlindon et al., 2014) (Figure 1.1).

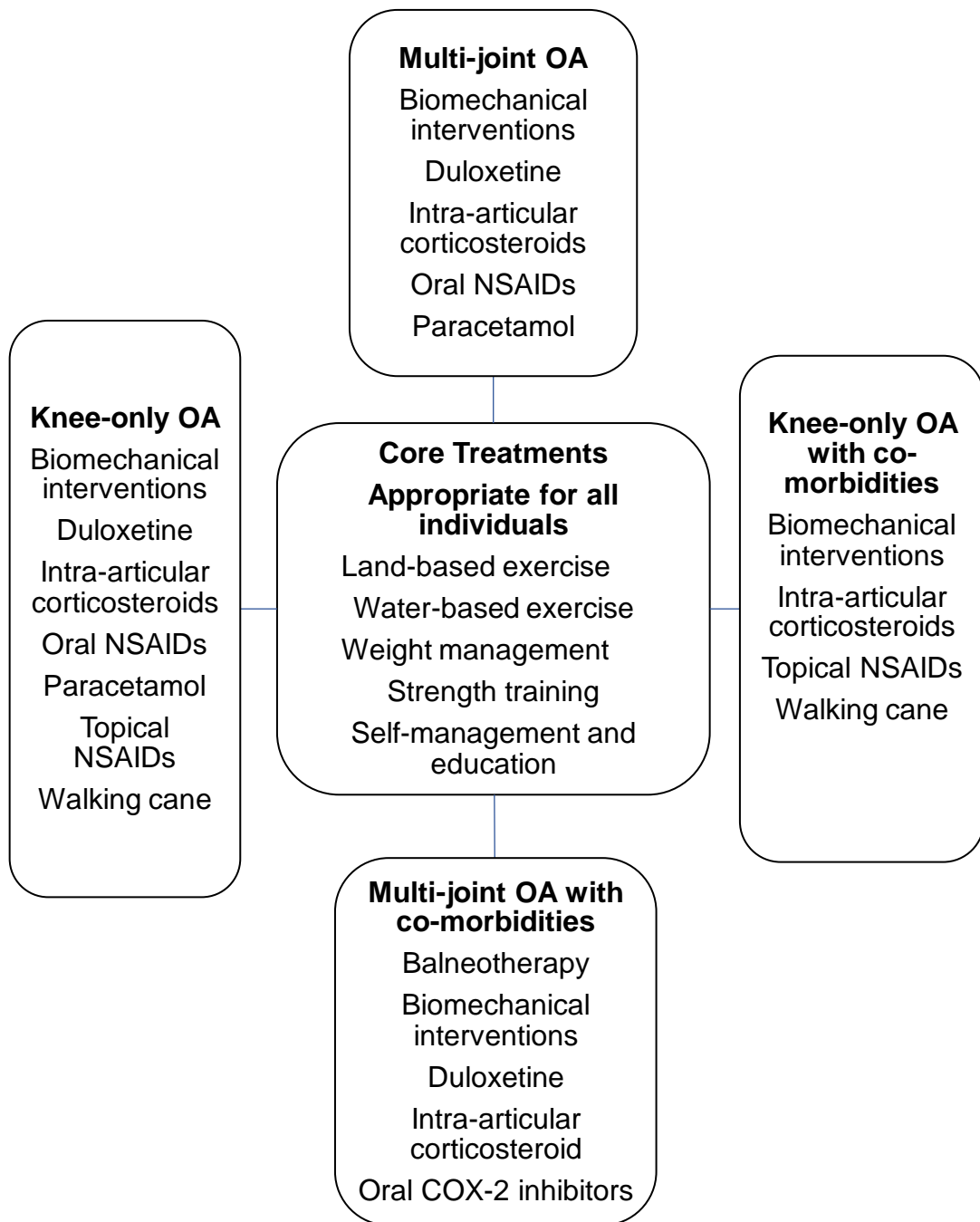


Fig. 1.1

OARSI guidelines for the non-surgical management of knee OA

Surgical interventions are used as a last resort for management of knee OA. Knee arthroscopy is a minimally invasive procedure used for removal of loose bodies and debridement of loose articular cartilage (Kirkley et al.,

2008). A recent systematic review on the effectiveness of knee arthroscopy versus conservative management of patients with degenerative knee disease reported that patients who underwent knee arthroscopy reported very small reductions in pain in the short term, but had no additional benefit as compared to conservative management in the long term (Brignardello-Petersen et al., 2017).

TKR is the recommended treatment for end-stage knee OA in patients who are not getting adequate pain relief and functional improvement from conservative treatment (Nelson et al., 2014; Zhang et al., 2008). However, dissatisfaction with TKR ranges from 18.6% to 25% (Baker et al., 2007; Beswick et al., 2012; Bourne et al., 2010; Gandhi et al., 2008; Scott et al., 2010). Dissatisfaction after TKR could be due to patient expectations not being met and, continued pain and limitation in physical function after joint replacement (Wylde et al., 2007).

1.2.2. Persistent post-surgical pain

Persistent post-surgical pain (PPSP) has been defined by the IASP to be pain that has developed after surgery, has been present for at least 2 to 3 months, and is independent of any pre-existing pain condition (IASP, 1986; Macrae & Davies, 1999; Merskey & Bogduk, 1994).

PPSP has been reported in a proportion of patients following several common surgical operations, such as thoracotomy, mastectomy, amputation, coronary artery bypass surgery, inguinal hernia repair, hysterectomy, caesarean section and total hip/knee replacements (Hickey et al., 2011; Kehlet et al., 2006; Recker & Perry, 2011; Vilardo & Shah, 2011).

The incidence of PPSP varies across different surgeries due to the different patient populations and surgical techniques. For example, performing a thoracotomy usually involves the separation of ribs or the resection of part of a rib which can then lead to injury to the intercostal nerves (Kehlet et al., 2006). Another example is breast surgery, where persistent post-mastectomy pain is commonly attributed to axillary node dissection, intercostobrachial nerve injury, or nerve injury as a result of chemotherapy and/or radiotherapy (Macrae, 2008; Perkins & Kehlet, 2000). A systematic review reported the

incidence of persistent pain after thoracotomy as 47%, persistent pain after breast surgery ranges from 11-57%, persistent pain after amputation ranges from 30-81%, persistent pain after cholecystectomy ranges from 3-56%, and persistent pain after inguinal hernia surgery as 11.5% (Perkins & Kehlet, 2000). Macrae (2008) estimated the incidence of persistent post-surgical pain for mastectomy to range from 20-50%, caesarean section at 6%, amputation from 50-85%, cardiac surgery from 30-55%, hernia repair from 5-35%, cholecystectomy from 5-50%, hip replacement at 12% and thoracotomy from 5-65%.

Several studies have investigated factors that predict development of PPSP. In a prospective study of risk factors for PPSP following hysterectomy, Pinto et al. (2012) reported that preoperative anxiety, pain catastrophizing and emotional illness representations (emotions in response to the illness underlying the need for surgery) as being the most significant predictive factors for the development of PPSP 4 months after hysterectomy. Poleshuck et al. (2006) investigated predictive risk factors for development of PPSP following breast cancer surgery. They reported that younger age was a significant predictor of developing PPSP 3 months after surgery. Predictive factors for higher pain levels for PPSP following breast cancer surgery were more invasive surgery, higher acute postoperative pain and radiation therapy after surgery (Poleshuck et al., 2006). In persistent post-thoracotomy pain, female gender and higher pain levels at first postoperative day were the most significant predictors of persistent pain (Gotoda et al., 2001).

Table 1.2 lists the risk factors for development of persistent post-surgical pain.

Table 1.2: Risk factors for persistent post-surgical pain.

Risk factors for persistent post-surgical pain		
Pre-Operative	Intra-Operative	Post-Operative
• Age	• Anaesthetic technique	• High levels of acute post-operative pain
• Chemoradiotherapy	• Surgical technique	• Anxiety
• Genetic predisposition		• Depression

•Female gender	•Excessive tissue	•Pain catastrophising
•Depression	damage (e.g. Nerves,	•Chemoradiotherapy
•Anxiety	muscles, soft tissues)	•Ongoing inflammatory
•Pain catastrophising		response
•High levels of pain		
•Chronic pain		
•Fear related to		
surgery		
•Neuropathic pain		
•Workers'		
compensation		
•Repeat surgery		

Based on Bruce and Quinlan (2011); Cregg et al. (2013); Kehlet et al. (2006) and Macrae and Davies (1999)

1.2.2.1. Total knee replacement

Total knee replacement (TKR) is a surgical procedure commonly used to manage chronic knee pain and improve physical function in those with knee OA, with 41,810 surgeries performed in Australia in 2012 (Australian Orthopaedic Association National Joint Replacement Registry [AOANJRR], 2013) at a cost ranging from \$18,874 to \$23,702 per surgery in a public hospital (Independent Hospital Pricing Authority, 2013). Although many patients report good outcomes, (Brander et al. (2003) reported that 86.9% did not report significant pain at 1 year post-TKR surgery; Puolakka et al. (2010) reported that 65% did not report significant pain at a minimum of 4 months (maximum of 22 months) after TKR surgery; Wylde et al. (2011) reported that 56% did not have any pain at 3-4 years following TKR surgery), a proportion of patients continue to report significant and persistent pain following TKR (Baker et al., 2007; Beswick et al., 2012; Brander et al., 2003; Puolakka et al., 2010; Wylde et al., 2007; Wylde et al., 2011).

1.2.2.2. Prevalence of persistent pain post-TKR

The prevalence of persistent pain post-TKR has been shown to range from 13.1% to 44% (Baker et al., 2007; Brander et al., 2003; Puolakka et al., 2010; Wylde et al., 2011). The reason for this wide variance is due to the different levels of pain reported in the studies. For example, in the study by Brander et al. (2003), they reported that in a study of 116 TKR subjects 13.1% reported significant (Visual Analogue Scale >40) pain at 12 months post-operatively; Wylde et al. (2011) found that 44% of TKR patients reported having persistent post-surgical pain of any severity (mild to severe-extreme), with 15% reporting severe-extreme persistent post-surgical pain at between 3 to 4 years post-operatively.

1.2.2.3. Causes of pain post-TKR

Mandalia et al. (2008) suggested that the causes of pain post-TKR could be broadly divided into intrinsic and extrinsic factors, with the common causes of pain being infection, haemarthrosis, instability, and patellofemoral problems.

- Infection

Infection following TKR is very rare and the incidence rate ranges from 0.4% to 2% (Austin et al., 2004; Blom et al., 2004; Mahomed et al., 2005; Namba et al., 2013; Wilson et al., 1990; Windsor & Bono, 1994).

- Haemarthrosis

Haemarthrosis after TKR ranges from 0.3% to 1.6% (Kindsfater & Scott, 1995; Ohdera et al., 2004; Oishi et al., 1995; Worland & Jessup, 1996).

- Instability

Knee prosthesis instability accounts for up to 22% of revision TKR surgery (Parratte & Pagnano, 2008; Rodriguez-Merchan, 2011). Instability may be due to several factors such as improper intra-operative ligamentous balancing, malalignment of prosthesis, loosening of the components and collapse (Toms et al., 2009).

- Patellofemoral Pain Syndrome (PFPS)

The incidence rate of PFPS has been reported to range from 2% to 7% (Scuderi et al., 1994).

A prospective study of persistent pain post-TKR demonstrated that 13.1% of TKR patients reported unexplained pain at 1 year post-TKR (Brander et al.,

2003). Hence, it appears that in a certain proportion of TKR patients there is no clear, structural cause for their persistent post-surgical pain.

1.2.2.4. Proposed risk factors / predictors

A number of other studies have identified pre-operative, intra-operative and post-operative risk factors that can lead to the development of persistent pain post TKR (Table 1.3).

A prospective study investigating predictors of poor outcome after TKR reported that at 5 years following surgery, the incidence of unexplained moderate to severe pain was 6% (Elson & Brenkel, 2006). The investigators reported that younger age (below 60 years), performing a lateral release and posterior cruciate ligament sacrifice were significant predictors of poor outcomes at 5 years following TKR.

Lingard et al. (2004) examined the preoperative predictors of persistent pain and functional outcome following TKR, and reported that higher levels of pre-operative pain and functional limitation were the strongest predictors of poor outcomes at 1 and 2 years following TKR. The investigators also reported that a higher number of comorbid medical conditions and a low mental health score pre-operatively were significantly associated with poor outcomes.

Abeloff et al. (2000) defines psychological distress as, “the general concept of maladaptive psychological functioning in the face of stressful life events”. In the scientific literature, psychological distress can include post-traumatic stress disorder, depression, anxiety, pain catastrophisation and stress (Belfer et al., 2013; Masselin-Dubois et al., 2013; Ross et al., 2015; Skogstad et al., 2014; Vilardo & Shah, 2011; Vincent et al., 2015). Psychological distress is a frequent feature of patients afflicted with persistent post-surgical pain (Belfer et al., 2013; Jeffery et al., 2011; Masselin-Dubois et al., 2013; Vilardo & Shah, 2011; Wylde et al., 2011).

Pre-operative depression has been found to be a significant predictor of higher post-operative resting and movement pain in TKR (Rakel et al., 2012). Depression has also been associated with higher non-steroidal anti-inflammatory drug use after primary TKR (Singh & Lewallen, 2012). A study on patients with anxiety and depressive symptoms prior to having a total hip or knee replacement found that they had worse patient reported outcomes

and were less satisfied than controls at 3 and 6 months post-operatively (Duivenvoorden et al., 2013).

Brander et al. (2003) conducted a prospective study to assess the predictive value of clinical and radiographic variables in the development of persistent pain post-TKR. They reported that pre-operative depression and anxiety were significant predictors of poor pain outcomes at 1 year post-TKR. The results of the study also demonstrated that high levels of pre-operative pain predicted poorer function at 1 year post-TKR.

Another prospective cohort study on the predictors of outcome following TKR reported that high levels of pre-operative pain and functional limitations predicted poor outcomes, with pre-operative depression and anxiety also being significant predictors of persistent pain at 6 months post-TKR (Judge et al., 2012). Of interest is the report that increased age, female gender and a higher body mass index predicted poor functional outcomes but not pain. Riddle et al. (2010) investigated the influence of psychological factors in predicting persistent pain post-TKR. The investigators reported that pain catastrophizing was the only consistent predictor of pain at 6 months after TKR.

Masselin-Dubois et al. (2013) investigated the psychological predictors of persistent postsurgical pain in 2 surgical models (TKR and breast surgery for cancer), the results demonstrated that regardless of surgical model; older age, high levels of post-operative pain, state anxiety and pain magnification predicted presence of persistent pain at 3 months following surgery.

A study which investigated acute post-operative pain at rest after hip and knee arthroplasty found that 44-57% of TKR patients woke up because of pain over the study period (post-operative days 1 – 3) (Wylde et al., 2011). The same study found that TKR patients who were woken by pain had significantly higher overnight pain scores as compared to those not woken by their pain each night (Wylde et al., 2011).

Creameans-Smith et al. (2006) investigated sleep disruptions in patients undergoing TKR and found that patients who reported more post-operative sleep disruptions had more pain at 1 month post-TKR and more functional limitations at 3 months post-TKR.

Based on the current research, psychological distress, functional limitation and pre-operative pain levels appear to be the most important predictors of persistent pain post-TKR. There is also ample evidence to indicate that sleep and pain are related. However, the mechanisms are still not fully understood. Hence more research is needed on the influence of sleep disturbance in the development of persistent post-surgical pain.

Table 1.3: Risk factors for persistent post-surgical pain after TKR.

Risk factors for persistent post-surgical pain after TKR		
Pre-Operative	Intra-Operative	Post-Operative
<ul style="list-style-type: none"> • Age • Female gender • Depression • Anxiety • Pain catastrophising • High levels of pain • Lower functional capacity • Pain sensitivity • Presence of comorbid medical conditions 	<ul style="list-style-type: none"> • Excessive tissue damage (e.g. Nerves, muscles, soft tissues) • Surgical approach (eg PCL sacrifice, lateral release) 	<ul style="list-style-type: none"> • High levels of acute post-operative pain • Anxiety • Depression • Pain catastrophising • Sleep quality

Based on Brander et al. (2003); Cremeans-Smith et al. (2006); Elson and Brenkel (2006); Fortin et al. (1999); Hawker et al. (2010); Judge et al. (2012); Lingard et al. (2004); Riddle et al. (2010); Vilardo and Shah (2011); Wilcox et al. (2000) and Wylde et al. (2011)

Pre-existing pain conditions

A systematic review identified pre-operative pain in the operating field and chronic pre-operative pain elsewhere as being predictors of persistent pain post-surgery (Althaus et al., 2012). The presence of previous pain has also been shown to be strongly associated with the development of chronic neuropathic pain (Kehlet et al., 2006). Widespread pain sensitisation in OA patients has been found to be associated with the development of persistent

pain post-TKR (Lundblad et al., 2008; Wylde et al., 2013). Presence of widespread pain sensitisation has also been documented in individuals suffering from persistent pain post-TKR (Skou et al., 2013).

'New' pain after TKR

Several groups have attempted to categorize persistent post-TKR pain in order to better manage poor outcomes. The UK-based Support and Treatment After Replacement (STAR) Expert Group (<http://www.bristol.ac.uk/clinical-sciences/research/musculoskeletal/orthopaedic/research/star>), based at the University of Bristol involves pain researchers from across Europe, Canada and Australia and has proposed 5 relatively distinct post-operative presentations (personal communication from Prof Anthony Wright, advisory group member). These are neuropathic pain, painful instability, proximal tibial tenderness, patellofemoral pain and chronic pain syndromes (i.e. widespread pain sensitisation and complex regional pain syndrome).

- Neuropathic pain

A number of studies support the presence of neuropathic-type symptoms. The prevalence of probable/definitive neuropathic pain in total knee arthroplasty/total hip arthroplasty patients with persistent post-surgical pain is about 5.7% (Haroutiunian et al., 2013). Two recent studies have found that close to 20% of knee OA sufferers reported components of neuropathic pain, using the PainDETECT questionnaire (Hochman et al., 2011; Ohtori et al., 2012). Albayrak et al. (2016) investigated risk factors for persistent pain following TKR and found that patients with persistent pain post-TKR scored higher in the PainDETECT questionnaire as compared to TKR patients without persistent pain. Cold hyperalgesia is a clinical feature commonly exhibited in neuropathic pain (Baron et al., 2010), and has been documented in the literature to be a prognostic factor for the development of chronic pain and disability in some musculoskeletal conditions such as whiplash associated disorder (Goldsmith et al., 2012; Maxwell & Sterling, 2013) and lateral epicondylalgia (Coombes et al., 2012). It has been proposed that the presence of widespread cold hyperalgesia alongside self-reported

neuropathic pain may particularly reflect excessive central sensitisation in OA (Gwilym et al., 2009; Hochman et al., 2013).

- Proximal tibial tenderness

Proximal tibial tenderness affects patients who have had a uni-compartmental knee replacement (Simpson et al., 2009), although this usually resolves within 12 months post-operatively due to bone remodeling (Simpson et al., 2009).

- Patellofemoral pain

The causes of patellofemoral pain following TKR are still largely unknown, however patellar mal-tracking and femoral component mal-rotation are believed to be the key causes (Dennis et al., 2011; Mosis et al., 2009; Muñoz-mahamud et al., 2011).

- Chronic pain syndromes

Chronic pain syndromes that have been reported post-TKR include complex regional pain syndrome and widespread pain sensitisation. Complex regional pain syndrome (CRPS) is characterized by pain in combination with sensory, autonomic, trophic and motor abnormalities (Marinus et al., 2011). Aberrant inflammatory mechanisms, vasomotor dysfunction and maladaptive neuroplasticity have been identified as the three major pathophysiological pathways of CRPS (Marinus et al., 2011). The incidence rate for CRPS after TKR has been stated to be 0.8% (Burns et al., 2006). Skou et al. (2013) found that patients with chronic pain after revision TKR surgery have significantly more pain sites, reduced mechanical pain thresholds and tolerance, as well as impaired conditioned pain modulation as compared to controls.

1.3. Conclusion

A recent knee OA study that compared QST measures of central sensitisation in 20 participants before and after TKR reported that these measures 'normalised' approximately 20 weeks post-surgery. The authors hypothesized that this return to normal values after removal of damaged tissue supports the notion that central pain processes in knee OA are maintained by peripheral nociceptive input (Graven-Nielsen et al., 2012). However, this should mean that knee OA pain should always be eliminated

with TKR surgery, provided that they have no other pre-existing chronic pain conditions. Yet, the prevalence of persistent pain post-TKR has been shown to range from 13.1% to 44% (Baker et al., 2007; Brander et al., 2003; Puolakka et al., 2010; Wylde et al., 2011).

Suokas et al. (2012) stated “the complexity of OA pain means that treatments targeting one specific mechanism may have low efficacy if offered to people whose pain is largely mediated by other mechanisms”. This could possibly explain the seemingly high rates of persistent pain post-TKR.

Persistent pain post-TKR: Pre-existing versus ‘new’ pain

Looking at all the available literature on persistent pain post-TKR, it is possible that persistent pain post-TKR may reflect ‘new’ pain resulting from the surgical intervention or may reflect lack of success in the detection or resolution of pre-existing, ‘old’ pain conditions. Development of a screening protocol that identifies patients who will not gain maximal benefit from undergoing a TKR will enable clinicians to (i) use suitable interventions that could help resolve the pre-existing pain conditions before TKR, hence reducing the risk of developing persistent pain post-TKR, or (ii) try a different approach to conservative management. The research reported in this thesis has used a range of measures to comprehensively screen patients to determine which measures are most strongly linked to the development of persistent pain post-TKR.

Chapter 2

Study 1

Quantitative Sensory Testing identifies patients with poor outcomes one year following Total Knee Replacement

2.1. Abstract

Background and Aims

Total knee replacement (TKR) is a standard intervention for individuals with painful osteoarthritis. Yet up to 15% of patients report severe persistent postsurgical pain. Poor outcomes following TKR may be attributed to various causes including infection or prosthetic instability, however it has been suggested that the presence of widespread pain/hyperalgesia and/or report of neuropathic-type pain may also be important predictors of ongoing pain. This study aimed to determine whether patients with persistent pain post TKR exhibit widespread hyperalgesia, sensory deficits and/or features of neuropathic pain.

Method

A cross sectional design was used. Fifty-three participants, 12-36 months following TKR surgery were divided into 'good outcome' and 'poor outcome' groups, based on Knee Society Score one year post surgery. Group differences in mechanical and thermal detection and pain thresholds at local and distant test sites and self-report of neuropathic-type pain, pain quality, comorbid conditions, health status and function were investigated.

Results

At the knee, significant group differences were found for pressure pain threshold (PPT) ($p=0.024$), heat detection threshold (HDT) ($p=0.009$) and cold pain threshold (CPT) ($p=0.008$). At the elbow, significant differences were similarly found for PPT ($p=0.002$), HDT ($p=0.01$), CPT ($p=0.01$), heat pain threshold (HPT) ($p=0.034$) and cold detection threshold (CDT) ($p=0.034$). There were also significant group differences for self-reported neuropathic pain (PainDETECT ($p=0.001$)), pain quality (PQAS subscores: paroxysmal

($p=0.008$), superficial ($p=0.025$), deep ($p<0.001$)), health status (EQ-5D ($p=0.018$), EQ-5D Health Score ($p=0.03$)) and disease specific questionnaire scores (WOMAC total ($p<0.001$), pain ($p<0.001$), stiffness ($p<0.001$) and function ($p<0.001$)).

Conclusion

Individuals with poor outcomes exhibited widespread mechanical and cold hyperalgesia, sensory deficits and higher levels of neuropathic-type pain. These findings may indicate that neuropathic pain and/or persistent central sensitization may be an important driver of persistent pain following joint replacement surgery.

2.2. Overview, Aims and Objectives

Knee arthroplasty is a widely-applied intervention which aims to relieve the pain and disability of osteoarthritis by replacing the weight-bearing surfaces of the knee joint. In 2009-2010, a total of 97,213 total knee replacement (TKR) surgeries were performed in Australia (AIHW, 2011). 719,000 in the United States of America (Centers for Disease Control and Prevention, 2011) and 76,497 in England and Wales in 2012 (National Joint Registry, 2013). Although most patients achieve substantial pain relief and improved function following TKR a proportion continue to experience significant persistent pain many years post-surgery. Persistent postsurgical pain is defined by the International Association of the Study of Pain as pain that develops after surgical intervention and lasts at least 2 months, with other causes of pain being excluded, particularly pain from a condition preceding the surgery (Macrae & Davies, 1999). A recent UK study (Wylde et al., 2011) reported that 44% of patients may be affected by persistent postsurgical pain at 3 to 4 years, although much of the pain was mild in severity, infrequent and an improvement from preoperative pain. Of concern, though is the 15% of TKR patients in this study who reported severe to extreme persistent postsurgical pain (Wylde et al., 2011). Such poor outcomes could be attributed to factors such as post-operative infection or prosthesis instability, but may also be influenced by preoperative factors such as presence of neuropathic-type pain or presence of widespread pain sensitivity. These latter factors suggest pre-existing altered central pain processing, which in some patients creates the potential for persistent post-operative pain.

The presence of neuropathic-type pain or widespread hyperalgesia has been reported in patients with knee OA in several recent studies. Hochman et al (2011) reported that more than 19% of an unselected community based sample of individuals with chronic OA had features of neuropathic pain according to the PainDETECT questionnaire. A more recent study confirmed this finding; with 43% of participants with knee OA reporting significantly higher scores on PainDETECT (Wright et al., 2017). This group also exhibited widespread cold hyperalgesia and increased sensitivity to pressure pain, which are clinical features often associated with neuropathic pain states

(Wright et al., 2017). King et al. (2013) presented similar findings, reporting that high symptom severity knee OA sufferers demonstrated reduced heat pain thresholds as compared to low symptom severity knee OA sufferers and controls. The investigators also reported that after controlling for the temperature for heat pain threshold and heat pain tolerance, high symptom severity knee OA sufferers had greater pain with experimental heat pain threshold and heat pain tolerance at a distant site (forearm), and greater pain with experimental heat pain threshold at the affected knee as compared to a low symptom severity knee OA group and controls. High symptom severity knee OA sufferers also demonstrated reduced mechanical pain thresholds at both distant sites (forearm, trapezius muscle and quadriceps muscle) and the affected knee as compared to controls (King et al., 2013). Similarly, Wylde et al. (2012) found that 71% of knee OA patients in their study had at least one sensory abnormality (hypoesthesia or hyperalgesia) as compared to normal controls.

Widespread hyperalgesia has been shown to occur in patients with painful knee OA in a number of studies, with a significant moderate to large correlation found between widespread mechanical hyperalgesia and self-reported pain (Arendt-Nielsen et al., 2010; King et al., 2013; Wright et al., 2017). It therefore appears that some patients with OA exhibit features potentially associated with a neuropathic pain phenotype and it is possible that they may be predisposed to ongoing post-operative pain.

Treede et al. (2008) proposed a grading system with 4 criteria in the evaluation of neuropathic pain in individuals (Table 2.1).

Table 2.1: Grading system for neuropathic pain

Grading system for neuropathic pain	
1	Pain with a distinct neuroanatomically plausible distribution
2	A history suggestive of a relevant lesion or disease affecting the peripheral or central somatosensory system
3	Demonstration of the distinct neuroanatomically plausible distribution by at least one confirmatory test

4 Demonstration of the relevant lesion or disease by at least one confirmatory test

The levels of certainty of presence of neuropathic pain is determined by the number of fulfilled criteria in an individual (Treede et al., 2008):

- Possible neuropathic pain
 - Criteria 1 and 2 fulfilled
- Probable neuropathic pain
 - Criteria 1 and 2, plus either 3 or 4 fulfilled
- Definite presence of neuropathic pain.
 - All 4 criteria fulfilled

Based on the current research, it can be postulated that a proportion of knee OA sufferers fit the criteria for probable neuropathic pain.

The aim of this study was to determine whether patients with persistent pain post-TKR exhibit widespread hyperalgesia, sensory deficits and/or features of neuropathic pain.

The objective of this study was:

1. To investigate whether there is a difference between measures of pain, function, health status and quantitative sensory testing (QST) between the 'no pain (good outcome)' and 'moderate to severe pain (poor outcome)' groups.

2.3. Research Hypotheses

2.3.1. Primary Hypothesis:

1. There will be a difference in measures of pressure pain threshold (PPT), thermal (heat and cold) pain and detection thresholds (heat and cold), and self-reported pain (neuropathic pain and pain quality) between participants categorized as having a good outcome following TKR surgery versus those classified as having a poor outcome.

2.3.2. Secondary Hypotheses:

1. There will be a difference in self-reported health status, comorbid conditions and function between participants categorized as good outcome versus the poor outcome group.
2. There will be a difference in self-reported pre-operative pain and function between participants categorized as good outcome versus the poor outcome group.

2.4. Methods

2.4.1. Participants

All participants were recruited as volunteers within 12-36 months of their TKR surgery from patients listed on the Joint Replacement Assessment Clinic (JRAC) registry at Royal Perth Hospital in Western Australia. Suitable patients were identified by JRAC staff but no RPH staff were involved in direct recruitment of participants.

Volunteers with numbness around the knee, haemophilia or previous history of stroke were excluded from the study because those factors can possibly influence the perception of thermal and pressure stimuli. Volunteers with limited understanding of English were also excluded. Inclusion and exclusion criteria were as in Table 2.2.

Table 2.2: Inclusion / Exclusion criteria

Inclusion Criteria	<ul style="list-style-type: none">• Above 50 years old• Underwent primary uni-lateral TKR because of OA, at least 12 months ago• Indicated either no pain (none) or moderate to severe pain (moderate-occasional, moderate-continuous, or severe) during the previous 4 weeks on the pain component of the Knee Society Score• Good comprehension of English language
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- Exclusion Criteria**
- Recent surgery (<6 months) in the contralateral knee and/or ipsilateral elbow
 - Indicated mild pain during the previous 4 weeks on the pain component of the Knee Society Score
 - Any cognitive impairment
 - Any neurological conditions (i.e. previous stroke)
 - Numbness around the knee and/or ipsilateral elbow
 - Haemophilia
-

All participants were advised to continue with their usual medications prior to attending the assessment session.

All participants provided written informed consent before participating in the study. Ethical approval was granted by Royal Perth Hospital Medical Research Ethics Committee (Approval Number 2012/117) and Curtin University Human Research Ethics Committee (Approval Number PT217/2012).

2.4.2. Study Design and Procedure

This study used a cross-sectional design. All participants were asked to attend a single assessment session. Once informed consent was obtained, each participant completed five self-report questionnaires and then underwent the quantitative sensory tests in standardised order. Additional pre-operative WOMAC data were collected for each participant from their JRAC documentation.

The research assessment was conducted at a single time for each participant, between 12 and 36 months after their TKR surgery, although their categorization was based on the pain component of the Knee Society Score (KSS) at the 12 month JRAC follow-up. The pain component of the KSS is categorized as no pain (none), mild or occasional pain (stairs only, walking and stairs), moderate pain (occasional, continual), and severe pain (Insall et al., 1989). Participants who had no pain were allocated to the good outcome group, and those with moderate to severe pain were allocated to the poor outcome group. Individuals reporting mild or occasional pain were not

included in the study. No pre-operative assessment was performed in this cross-sectional study.

2.4.3. Outcome Measures

Self-Reported Measures:

All participants completed a paper version of the questionnaires on the day of their research assessment. The questionnaires were as stated below.

Disease-specific

1. **Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)** is a disease-specific self-report measure designed for standardised reporting of pain and function in individuals with knee or hip osteoarthritis (Bellamy, 1989). It consists of 24 items divided over 3 subscales: pain, joint stiffness and physical function. The WOMAC index has demonstrated good internal validity (Cronbach's Alpha: 0.92 for pain subscale; 0.90 for stiffness subscale; 0.98 for physical function subscale) (Jinks et al., 2002), good test-retest reliability ($ICC_{2,1}$: 0.88; 95% CI: -0.40 to 1.81 for pain subscale, $ICC_{2,1}$: 0.69; 95% CI: -0.84 to 0.55 for stiffness subscale, $ICC_{2,1}$: 0.85; 95% CI: -1.47 to 6.3 for physical function subscale) (Jinks et al., 2002), responsiveness to change (RE: 0.98; 95% CI: -37.0 to -26.2 for pain subscale, RE: 0.66; 95% CI: -31.5 to -20.6 for stiffness subscale, RE: 1.00; 95% CI: -34.1 to -24.2 for physical function subscale) (Ackerman et al., 2006), and acceptable construct validity (McConnell et al., 2001).

Health status

2. **European Quality of Life Questionnaire (EQ-5D)** represents an estimation of the patient's perceived quality of life and state of health (Busschbach et al., 1999). The EQ-5D demonstrated moderate test-retest reliability (EQ-5D_{vas} ICC: 0.70; 95% CI: 0.60-0.80; EQ-5D_{utility} ICC: 0.73; 95% CI: 0.63-0.83) and acceptable validity (Hurst et al., 1997).

Comorbid Conditions

3. **Self-Administered Comorbidity Questionnaire (SCQ)** assesses for the presence of 12 medical conditions for people with no prior medical

knowledge (Sangha et al., 2003). There are an additional 3 optional questions regarding any other medical conditions. The SCQ demonstrated good test-retest reliability (ICCs: 0.94; 95% CI: 0.72 to 0.99) and acceptable validity (Sangha et al., 2003).

Pain

4. **PainDETECT** is a self-report screening tool to identify features of neuropathic pain (Freynhagen & Baron, 2006). It consists of 9 items over 3 categories: pain quality, pain pattern and pain radiation. The questionnaire is a reliable screening tool with good internal consistency (Cronbach's Alpha: 0.83), high sensitivity (85%), specificity (80%) and positive predictive accuracy (83%) of a neuropathic pain component being present in chronic low back pain sufferers (Freynhagen & Baron, 2006). It has also been used in a number of studies looking at the presence of neuropathic pain components in other musculoskeletal conditions including osteoarthritis (Gwilym et al., 2011; Jespersen et al., 2010; Ohtori et al., 2012; Shigemura et al., 2011).
5. **Pain Quality Assessment Scale (PQAS)** is used to provide additional data regarding the dimensions of spontaneous pain experienced by participants (Victor et al., 2008). The PQAS was developed by adding additional items to the 10-item Neuropathic Pain Scale (NPS) (Jensen, 2006). The 10 NPS items have been shown to have adequate discriminant validity (Pearson's r : 0.05 to 0.73) and predictive validity (Galer & Jensen, 1997). The PQAS is able to provide more comprehensive information about pain quality than alternative one-dimensional pain scales (Jensen et al., 2012). It has also been shown to have validity for assessing treatment-related changes in pain quality and spatial characteristics (Jensen et al., 2006). Factor analysis of the PQAS revealed 3 clear pain quality domains: (1) Paroxysmal pain, (2) Superficial pain and (3) Deep pain (Victor et al., 2008). The 3 pain quality domains have been shown to have adequate to good internal consistency (Cronbach's Alpha: Paroxysmal>0.80, Superficial= 0.73 and Deep=0.68) (Gould et al., 2009).

Quantitative Sensory Tests:

All quantitative sensory tests (QST) were performed at the medial joint line of the operated knee and over the ipsilateral extensor carpi radialis brevis (ECRB) muscle in the upper limb. The ECRB muscle has been used previously in other QST studies (Slater et al., 2003; Slater et al., 2005). The ECRB was located by using the standardized method as described by Riek et al. (2000). The quantitative sensory testing was conducted with the participant lying in a relaxed position on a plinth. The method of limits approach was used for the quantitative sensory tests stated below.

1. **Pressure Pain Threshold (PPT)** was measured using an electronic, digital algometer (Somedic, Sweden) with a 1cm² round rubber tip at the end connected to a pressure transducer within the handle of the unit. The algometer was applied at 90° angle to the skin at a constant rate of 40 kPa/sec. The subject was given a control switch and instructed to press the switch when the sensation changes from pressure to pain, at which time the test was terminated. PPT has been shown to have good test-retest reliability for the knee (ICC: 0.83; 95% CI: 0.72-0.90) and forearm (ICC: 0.86; 95% CI: 0.77-0.92) in OA patients (Wylde et al., 2011). 1 practice trial was followed by 3 measurements, with the mean calculated for analysis (Lacourt et al., 2012; Persson et al., 2004).
2. **Cold/Heat Detection and Pain Thresholds** were measured using a peltier thermode (Medoc, Israel). The minimum temperature was set at 0°C, and the maximum temperature set at 50°C. A 30x30mm contact probe was attached to the test site with a strap and the participant was given several minutes to adapt to the baseline temperature of 32°C. When the device was activated, the thermode temperature rose or fell at a rate of 1°C/sec. This rate of temperature change has been shown to reduce intra-individual variation (Palmer et al., 2000). The subject was given a control switch and instructed to press the switch when they perceived the relevant sensation (i.e. if it was a heat detection threshold test, the participant was instructed to depress the switch once they detected an increase in heat). The respective thermal detection thresholds were always tested before the thermal pain

thresholds to minimise sensitization of receptors by the noxious input. The thresholds were tested in the order of **cold detection threshold (CDT), cold pain threshold (CPT), heat detection threshold (HDT) and heat pain threshold (HPT)**. CDT has been demonstrated to have moderate test-retest reliability for the knee (ICC: 0.70; 95% CI: 0.53-0.82) and fair test-retest reliability for the forearm (ICC: 0.41; 95% CI: 0.15-0.62) in knee OA sufferers (Wylde et al., 2011). CPT has been demonstrated to have excellent test-retest reliability across several sites with ICCs ranging from 0.93 to 0.94 in healthy participants (Moss et al., 2016). HDT has been demonstrated to have moderate test-retest reliability for the knee (ICC: 0.70; 95% CI: 0.49-0.83) and fair test-retest reliability for the forearm (ICC: 0.52; 95% CI: 0.29-0.70) in knee OA sufferers (Wylde et al., 2011). HPT has been demonstrated to have moderate test-retest reliability for the knee (ICC: 0.77; 95% CI: 0.62-0.92) and excellent test-retest reliability for the forearm (ICC: 0.86; 95% CI: 0.76-0.92) in knee OA sufferers (Wylde et al., 2011). HPT demonstrated moderate test-retest reliability (ICC: 0.68; 95% CI: 0.55-0.79) in normals (Felix & Widerström-Noga, 2009). Each stimulus was separated by a randomised 3 to 6 second interval. For each threshold, 1 practice trial was followed by 3 measurements, with the mean calculated for analysis.

2.4.4. Power Analysis

Power calculations found that to detect a clinically relevant difference of 15% (β set at 0.80, $\alpha < 0.05$) between participants in the good outcome and poor outcome groups, a total sample of 56 was needed for pressure pain threshold and 50 for cold pain threshold. Given the considerably smaller standard deviations relative to means reported previously for heat pain threshold compared with pressure pain threshold or cold pain threshold (Hochman et al., 2013; Suokas et al., 2012; Wylde et al., 2013) a smaller sample size would suffice for HPT. A total sample size of 55 was considered adequate.

2.4.5. Data Analysis

IBM SPSS Statistics version 22 was used for the statistical analysis, with alpha set at 0.05. Normality of the data was determined by using the Shapiro-Wilk test, any variable that had $p > 0.05$ was considered normally distributed. Levene's test was used to confirm whether the data for each group demonstrated equal variance. Degrees of freedom were corrected when equal variances were not assumed ($p < 0.05$). Independent T tests were used to analyse group differences in pressure pain threshold and WOMAC data. The rest of the data were not normally distributed and so were analysed using Mann Whitney U tests. All data were reported as mean \pm standard deviation. Significant results were considered as $p < 0.05$. Table 2.3 shows the statistical tests for each hypothesis.

Table 2.3: Hypotheses and Statistical Test Used

Hypotheses and Related Data	Statistical Analysis
1. Difference in pressure pain threshold (PPT) between good outcome versus poor outcome groups.	Independent T-Test
2. Difference in thermal (cold and heat) pain and detection thresholds between good outcome versus poor outcome groups.	Mann Whitney U-Test
3. Difference in self-reported pain between good outcome versus poor outcome groups. PainDETECT PQAS	Mann Whitney U-Test
4. Difference in self-reported health status and function between good outcome versus poor outcome groups. WOMAC EQ5D SCQ PQAS	Independent T-Test Mann Whitney U-Test Mann Whitney U-Test Mann Whitney U-Test

2.5. Results

2.5.1. Participant demographics

A total of fifty-three participants took part in the study. Thirty-one participants in the good outcome group (thirteen male and eighteen female; mean age 69.9 ± 7.25 , range 53-85) and twenty-two participants in the poor outcome group (six male and sixteen female; mean age 69.8 ± 7.07 , range 51-79) (Table 2.4).

Table 2.4: Participant demographics

	Good outcome group (n = 31)	Poor outcome group (n = 22)
Gender (M : F)	13 : 18	6 : 16
Age (years)	69.9 ± 7.3	69.8 ± 7.1
Age (range)	53 to 85	51 to 79

2.5.2. Primary Hypothesis:

There will be a difference in measures of pressure pain threshold (PPT), thermal (cold and heat) pain and detection thresholds, and self-reported pain (neuropathic pain and pain quality) between the good outcome and the poor outcome groups.

- **Pressure Pain Threshold**

The poor outcome group exhibited significantly lower PPT than the good outcome group, both at the operated knee ($p=0.024$) and at the distant ECRB site ($p=0.002$) (Table 2.5).

Table 2.5: Pressure pain threshold (kPa)

Site	Good outcome		Poor outcome		p
	Mean	SD	Mean	SD	
Knee	417	255	283	168	0.024*
ECRB	454	168	314	140	0.002*

* Indicates statistical significance at $p \leq 0.05$

- **Cold Detection and Cold Pain Thresholds**

The poor outcome group perceived cold at a lower temperature (indicating a reduction in sensory acuity) than the good outcome group at the ECRB site ($p=0.034$).

The poor outcome group had significantly higher cold pain thresholds (increased cold pain sensitivity) than the good outcome group, both at the operated knee ($p=0.008$) and at the distant ECRB site ($p=0.01$) (Table 2.6).

Table 2.6: Cold detection and cold pain thresholds ($^{\circ}\text{C}$)

Site	Test	Good outcome		Poor outcome		p
		Mean	SD	Mean	SD	
Knee	CDT	26.3	3.9	24.2	7.0	0.259
	CPT	2.7	5.6	9.2	10.3	0.008*
ECRB	CDT	28.4	2.1	25.8	6.0	0.034*
	CPT	2.9	5.5	9.9	10.1	0.01*

* Indicates statistical significance at $p \leq 0.05$

- **Heat Detection and Heat Pain Thresholds**

The poor outcome group detected changes in heat sensation at significantly higher temperatures than the good outcome group both at the operated knee ($p=0.009$) and at the ECRB site ($p=0.01$) indicating the poor outcome group had reduced sensory acuity. Heat pain thresholds were not significantly different between groups at the knee ($p=0.168$), although at ECRB the poor outcome group exhibited significantly reduced heat pain thresholds (increased heat pain sensitivity) ($p=0.011$) (Table 2.7).

Table 2.7: Heat detection and heat pain thresholds ($^{\circ}\text{C}$)

Site	Test	Good outcome		Poor outcome		p
		Mean	SD	Mean	SD	
Knee	HDT	39.4	4.0	42.9	4.6	0.009*
	HPT	47.0	3.5	47.5	2.1	0.168
ECRB	HDT	38.0	3.7	42.1	5.5	0.010*
	HPT	48.5	2.1	44.3	10.7	0.011*

* Indicates statistical significance at $p \leq 0.05$

- **Self-reported pain (neuropathic pain and pain quality)**

PainDETECT

Those in the poor outcome group reported significantly higher levels of neuropathic-type pain as measured by PainDETECT ($p=0.001^*$) (Table 2.8).

Table 2.8: Self-reported neuropathic pain

	Good outcome		Poor outcome		p
	Mean	SD	Mean	SD	
PainDETECT	3.03	3.62	7.27	5.8	$=0.001^*$

* Indicates statistical significance at $p \leq 0.05$

PQAS

The poor outcome group also reported significantly higher scores in the various components of the PQAS as compared to the good outcome group. This difference was seen for all the subscores (paroxysmal: $p=0.008$, superficial: $p=0.025$, deep: $p<0.001$) (Table 2.9).

Table 2.9: PQAS subscores

	Good outcome		Poor outcome		p
	Mean	SD	Mean	SD	
Paroxysmal	0.58	1.23	4.45	7.1	0.008^*
Superficial	3.03	3.89	7.59	7.96	0.025^*
Deep	2.55	4.11	10.95	11.32	$<0.001^*$

* Indicates statistical significance at $p \leq 0.05$

2.5.3. Secondary Hypothesis 1:

There will be a difference in self-reported comorbid conditions, health status and function between participants categorized as good outcome versus the poor outcome groups.

- **Self-reported comorbid conditions and health status**

Comorbidity (SCQ), EQ-5D and EQ-5D Health Scores

There was no significant difference in the number of comorbidities between the good (5.71 ± 0.74) or poor (7.41 ± 0.94) outcome groups ($p=0.216$). However, those in the poor outcome group rated themselves as having a significantly lower quality of life ($p=0.018$): poor outcome group 2.27 ± 0.32 ; good outcome group 1.35 ± 0.35 . There was also a statistically significant difference ($p=0.03$) between the good outcome (82.52 ± 2.94) and poor outcome (73.77 ± 3.48) groups for the EQ-5D Health Scores, with the good outcome group rating themselves as being in a better state of health as compared to the poor outcome group (Table 2.10).

Table 2.10: Self-reported comorbid conditions and health status

	Good outcome		Poor outcome		p
	Mean	SD	Mean	SD	
SCQ	5.71	4.12	7.41	4.39	0.216
EQ-5D	1.35	1.92	2.27	1.49	0.018*
EQ-5D Health Scores	82.52	16.36	73.77	16.33	0.030*

* Indicates statistical significance at $p \leq 0.05$

- **Self-reported function**

WOMAC

The poor outcome group recorded significantly higher levels of pain, stiffness and dysfunction than those in the good outcome group: WOMAC-total ($p<0.001$); WOMAC-pain ($p<0.001$); WOMAC-stiffness ($p<0.001$); WOMAC-function ($p<0.001$) (Table 2.11).

Table 2.11: WOMAC

	Good outcome		Poor outcome		p
	Mean	SD	Mean	SD	

WOMAC Pain	2.13	2.46	5.77	3.96	<0.001*
WOMAC Stiffness	0.94	1.31	2.68	2.01	<0.001*
WOMAC Function	6.1	6.62	17.73	12.14	<0.001*
WOMAC Total	9.16	9.44	26.18	16.87	<0.001*

* Indicates statistical significance at $p \leq 0.05$

2.5.4. Secondary Hypothesis 2:

There will be a difference in self-reported pre-operative pain and function between participants categorized as good outcome versus the poor outcome groups.

- Self-reported pre-operative pain and function**

WOMAC

Due to incomplete/missing data from the RPH JRAC registry, preoperative WOMAC scores were only available for 44 of the participants (90% of the good outcome group but only 73% of the poor outcome group). There were no significant group differences in either the WOMAC total or any sub-score, although there was a trend towards higher scores for those in the poor outcome group (Table 2.12).

Table 2.12: Pre-operative WOMAC

	Good outcome		Poor outcome		p
	Mean	SD	Mean	SD	
WOMAC Pain	9.32	3.01	10.75	2.98	0.136
WOMAC Stiffness	4.11	1.77	4.5	1.63	0.471
WOMAC Function	29.46	11.86	33.06	7.92	0.286
WOMAC Total	42.89	15.46	48.31	11.59	0.23

* Indicates statistical significance at $p \leq 0.05$

When percentage change in WOMAC score from pre to post surgery was evaluated, a significant group difference was also seen, with those with good outcomes showing significantly greater change in WOMAC score (WOMAC

Pain ($p=0.004$), WOMAC Stiffness ($p=0.022$), WOMAC Function ($p=0.008$) and WOMAC Total ($p<0.001$)) than those with poor outcomes.

The good outcome group improved in all aspects of pain and function by an average of 78% from preoperative baseline, whereas those in the poor outcome group only improved by an average 45% (Table 2.13).

Table 2.13: Percentage change from mean pre-operative to mean post-operative WOMAC scores for good and poor outcome groups.

Good Outcome Group						
WOMAC	Pre-Op		Post-Op		Mean Difference	% change
	Mean	SD	Mean	SD		
Pain	9.32	3.01	2.12	2.46	7.2	77.2%
Stiffness	4.11	1.77	0.94	1.31	3.17	77.1%
Function	29.46	11.86	6.1	6.62	23.36	79.3%
TOTAL	42.89	15.46	9.16	9.44	33.73	78.6%
Poor Outcome Group						
WOMAC	Pre-Op		Post-Op		Mean Difference	% change
	Mean	SD	Mean	SD		
Pain	10.75	2.98	5.77	3.96	4.98	46.3%
Stiffness	4.5	1.63	2.68	2.01	1.82	40.4%
Function	33.06	7.92	17.72	12.14	15.34	46.4%
TOTAL	48.31	11.59	26.18	16.87	22.13	45.8%

Summary of Results

Hypotheses	Accepted/Rejected
1. There will be a difference in measures of pressure pain threshold, thermal pain and detection thresholds, and self-reported pain (neuropathic pain and pain quality) between participants categorized as good outcome versus the poor outcome groups.	Partially accepted
2. There will be a difference in self-reported health status, comorbid conditions and function between participants categorized as good outcome versus the poor outcome groups.	Partially accepted

3. There will be a difference in self-reported pre-operative pain and function between participants categorized as good outcome versus the poor outcome groups.	Rejected
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2.6. Discussion

This cross-sectional study aimed to use QST and self-report questionnaires to determine if patients with persistent moderate to severe pain one to three years following TKR surgery exhibited signs of widespread hyperalgesia, sensory deficits and neuropathic-type pain compared with those reporting no pain.

The prevalence of persistent pain following TKR has been shown to range from 13% to 44% and it is suggested that central augmentation of pain related to central sensitization and other factors may contribute to this persistent pain (Baker et al., 2007; Brander et al., 2003; Puolakka et al., 2010; Wylde et al., 2007; Wylde et al., 2011).

The presentation of pain in knee OA ranges from localised pain to widespread hyperalgesia (Arendt-Nielsen et al., 2010; Carlesso & Neogi, 2016; Graven-Nielsen et al., 2012; Imamura et al., 2008; Lundblad et al., 2008; Wylde et al., 2012; Wylde et al., 2013), the present study demonstrated that patients with a poor outcome following TKR surgery continue to present with both localised pain and widespread hyperalgesia. The present study found that those with poor outcomes had significantly different (sensitized) thresholds to pressure pain, cold pain and heat pain compared with the good outcome group.

Quantitative Sensory Testing

A systematic review of quantitative sensory testing in painful OA reported that individuals with painful OA had decreased PPTs at the affected joint and at a remote site (Suokas et al., 2012). Skou et al. (2013) investigated sensitization in patients after revision TKR and reported that patients with pain after revision TKR demonstrated both local and widespread mechanical

hyperalgesia as compared to patients without pain. The present study's findings of decreased PPTs at the operated knee and the distant ECRB in the poor outcome group reflect both the findings of Skou et al. (2013), and also the trend seen in the systematic review.

The poor outcome group also exhibited significantly impaired sensory acuity for cold and heat sensation detection at both the local operated knee site and at the unaffected and distant ECRB elbow site. This is an important finding that may be linked to the development of neuropathic pain.

Hyperalgesia that spreads beyond the affected site, in particular to a site in a different body region may suggest a centrally-driven mechanism which maintains pain, even in the absence of pathology (Latremoliere & Woolf, 2009). These findings are apparently at odds with Graven-Nielsen et al. (2012) and Martinez et al. (2007). Those studies found that the pre-operative hyperalgesia seen in knee OA patients normalizes following TKR. Martinez et al. (2007) investigated multi-modality hyperalgesia in a cohort of 20 patients scheduled for TKR and reported that the pre-operative thermal hyperalgesia and immediate post-operative thermal and mechanical hyperalgesia had normalized by 4 months post-TKR.

The study by Graven-Nielsen et al. (2012) did not specify whether the post-surgical PPT values had improved to normal levels and, since a mean of all 20 participants was used, there were no data exploring whether there were a proportion of patients who exhibited no reduction in mechanical hyperalgesia. A larger study would help to clarify this.

Self-Report Questionnaires

There were also group differences in the self-reported questionnaires. Although preoperative WOMAC values showed no significant differences between groups, only 73% of those in the poor outcomes group had preoperative data and there was a trend towards this group reporting higher levels of pain, stiffness and dysfunction. Postoperatively there was a clear group difference, as might be anticipated. However, when percentage change from pre to post surgical WOMAC scores was investigated, it became clear that those in the good outcome group exhibited significantly greater improvements. This group demonstrated close to an 80%

improvement in pain, stiffness and function, a result that compares very favourably with pharmacological studies that report improvements in WOMAC score ranging from 36% to 45% (Altman et al., 2007; Babul et al., 2004; Barthel et al., 2009; Kivitz et al., 2008; Williams et al., 2001). In contrast, those in the poor outcome group achieved only a 45% improvement in WOMAC scores following TKR surgery, strongly suggesting that this is a distinct group for whom removal of pathological tissue is not the complete solution in terms of pain reduction.

This difference in pain and function improvement post-surgery could not be explained by additional comorbid conditions in those reporting poor outcomes. SCQ scores showed that there were no significant group differences in the number of comorbid conditions. Nevertheless, the poor outcome group reported greater difficulties in activities of daily living and lower quality of life compared to the good outcome group following TKR surgery, according to EQ-5D score.

The significant group differences in values for the PainDETECT neuropathic pain questionnaire and the paroxysmal and superficial subscores of PQAS suggest that the quality of pain experienced by those with poor outcomes may differ and this would support the QST findings above. However, although patients with poor outcomes reported significantly higher levels of neuropathic-type pain symptoms on PainDETECT, none scored as positive for neuropathic pain and only 4 had scores in the intermediate classification of “unclear neuropathic”. This poor outcome group therefore did not exhibit clear signs of the neuropathic-type pain that has been proposed as an additional sign of centrally-driven pain sensitization (Woolf & Mannion, 1999).

Study Limitations

The limitations of this study must be acknowledged. Any cross-sectional study is limited by the inability to establish a temporal relationship between events and cannot determine causality, or the direction of any associations. Consequently, any findings need to be tested with a longitudinal study. The present study also suffered from difficulties with recruitment, particularly of

those with poor outcomes, for whom attending a potentially uncomfortable test session was too daunting. A larger sample size would increase the power of the study and may clarify the extent of neuropathic-type pain in those with poor outcomes. It is also worth pointing out some considerations regarding group allocation. The initial Knee Society Score was measured by JRAC at the standard one-year post-TKR assessment. However, this study recruited and tested participants at between 12 and 36 months post-op. Finally, participants in this study were not asked to wash out their usual pain medications prior to testing, a factor which is likely to have influenced both QST values and the questionnaire scores. The present study did not consider psychological factors or body mass index as additional factors that may predict unsatisfactory outcome following TKR and this would need to be addressed in a more comprehensive longitudinal study.

Implications

This small cross-sectional study has signaled that those with poor outcomes up to 3 years following their TKR surgery may experience pain that is driven by central mechanisms. A longitudinal study is clearly required, where participants are assessed for QST and neuropathic-type pain pre-operatively and then at various time points post-operatively. A wash out of all pain medications prior to testing at all time points would be essential to clarify the extent of hyperalgesia and pain quality. It has also been suggested that specific surgical procedures may be more likely to cause persistent pain (e.g. sacrificed cruciate ligament, lateral release and fat pad excision) and so should be noted as covariates in a future study (Elson & Brenkel, 2006; Meneghini et al., 2007).

2.7. Conclusion

In conclusion, this study found that patients reporting persistent moderate to severe pain at one year up following TKR report only a 45% improvement in pain, stiffness and function up to three years post-surgery. These participants also exhibit widespread mechanical and thermal hyperalgesia, impaired thermal sensation and report higher levels of neuropathic-type pain, although not at a level that is strongly indicative of neuropathic pain. Those with good

outcomes did not exhibit the same degree of hyperalgesia, sensory impairment or neuropathic-type pain and reported up to an 80% improvement in pain, stiffness and function following surgery. These findings support the hypothesis that peripheral nociceptive input is not the only process able to maintain central sensitization (Zusman, 2004), given that the source of peripheral nociceptive input has been removed as a result of the knee replacement surgery.

Chapter 3

Study 2

Sustained Cold Response

3.1. Abstract

Background and Aims

An individual's response to a cold stimulus may provide an indication of their overall pain sensitivity and may be linked to their risk of developing a persistent pain problem. Cold pain response is conventionally tested as the threshold temperature at which an individual starts to feel pain in response to a cooling stimulus. However, this approach is of limited usefulness in a clinic setting due to equipment expense and impracticality. Two alternative ways of testing cold response have been developed, one using a small thermode device set to a specific cool temperature that is placed on the skin and another using a previously validated menthol gel formulation that is spread on the skin. Both cold tests quantify response using a previously developed score that combines measures of intensity and measures of sensation quality, known as the Algotect Descriptor Index (ADI). This study aimed to assess the reliability and validity of these two methods, when compared to the conventional cold pain threshold testing. Correlations between each cold response test were also examined.

Method

A test-retest design was used, with forty-two healthy participants. The test-retest reliability of the sustained cold and topical menthol response tests were evaluated against a standard cold pain threshold test. The association between: (1) Sustained cold response and topical menthol response tests; (2) Sustained cold response test and cold pain threshold (CPT) were also examined. Lastly, the ability of sustained cold and topical menthol responses tests to identify an abnormal CPT response to cold were explored.

Results

Excellent test-retest reliability was demonstrated for the sustained cold response test (ICC: 0.855; 95% CI: 0.713-0.952), topical menthol response

test (ICC: 0.851; 95% CI: 0.739-0.917) and the standard testing of cold pain threshold (ICC: 0.941; 95% CI: 0.892-0.968). Positive correlations were also found between each cold response test; Algotect Descriptor Index (ADI)-sustained cold total and CPT temperature ($r=0.355$, $p=0.021$), ADI-sustained cold and ADI-topical menthol (Visual Analogue Scale (VAS) intensity ($r=0.458$, $p=0.002$), Mean Word Score (MWS) ($r=0.417$, $p=0.006$) and ADI total score ($r=0.500$, $p=0.001$)), and CPT temperature and ADI-topical menthol score (MWS subscore ($r=0.389$, $p=0.009$) and total score ($r=0.413$, $p=0.007$)).

This study showed no significant difference in CPT values between groups for the sustained cold response test, although there was a trend towards significance for difference in CPT values between topical menthol high and low value groups.

Conclusion

The results demonstrated the excellent reliability of the two alternative ways of testing cold response, and the positive correlations between the standard way of testing for cold pain response and the two alternative cold tests. The sustained cold and topical menthol responses were not able to significantly differentiate an abnormal CPT response to cold. However, we envisage that with a larger sample size, the topical menthol response test will be able to significantly differentiate participants with an abnormal response to cold.

3.2. Overview, Aims and Objectives

Thermal hyperalgesia has been shown to be a prognostic factor for the development of chronic pain and disability in some musculoskeletal conditions (Goldsmith et al., 2012; Staud et al., 2012). Cold hyperalgesia is an important feature in neuropathic pain states (Freeman et al., 2014), and has been proposed as a sign of widespread central sensitization (Woolf, 2011). Cold hyperalgesia has also been found in individuals who suffer from neck pain (Steinmetz & Jull, 2013), cervical radiculopathy (Tampin et al., 2012), temporomandibular disorders (Park et al., 2010), lateral epicondylalgia (Coombes et al., 2012), painful knee osteoarthritis (Moss et al., 2016; Wright et al., 2017), and in non-mechanical chronic non-specific low back pain (O'Sullivan et al., 2014). In whiplash injury, cold hyperalgesia is one of the factors that predicts increased rates of pain and disability (Sterling et al., 2005). Cold hyperalgesia has also been identified to be a consistent predictor of higher pain levels and disability in lateral epicondylalgia (Coombes et al., 2015). Elevated cold pain thresholds are also associated with increased pain and decreased function in patients with knee osteoarthritis (Wright et al., 2017). The current research evidence therefore suggests that the presence of cold hyperalgesia in some musculoskeletal conditions may predict poor outcomes.

Cold hyperalgesia however is rarely tested in the clinical setting. Available equipment is primitive and includes the use of metal rollers, test tubes filled with chilled water, ice or coolants (e.g. acetone) (Baron et al., 2010; Maxwell & Sterling, 2013; Uddin & MacDermid, 2016). Such methods of testing are imprecise, both in terms of being able to control the cold stimulus and in terms of the response provided by the patient. Use of ice or acetone is also problematic as the stimulus is supra-threshold for most individuals and so evaluation of an abnormally hyperalgesic response is difficult.

In scientific research, cold hyperalgesia is generally assessed using a computer-controlled peltier thermode, such as the TSA-II – Neurosensory analyzer produced by Medoc, Israel. Such quantitative sensory testing (QST)

devices are advantageous in research as they can generate repeatable and precise stimuli, however the cost and maintenance of these devices can prove prohibitive for healthcare organizations.

This study aimed to assess the reliability and validity relative to CPT testing of two simple, relatively inexpensive but precise ways of testing cold response that could potentially be used in a clinical setting. If found to be reliable, the cold response tests may be used to provide additional valuable information about pain system response for primary care practitioners.

The objectives of this study were:

1. To evaluate the test-retest reliability of the sustained cold response test (using a custom-made Dharma thermode set at 12°C and ADI) and menthol cold response test (using a pre-determined dose of topically-applied menthol and ADI) compared with standard cold pain threshold (CPT) reliability.
2. To evaluate whether the response to sustained cold correlates with the response to menthol cold.
3. To evaluate whether there is a correlation between CPT and response to sustained cold and between CPT and response to menthol cold.
4. To evaluate whether high or low sustained cold and menthol cold response could differentiate between high and low CPT temperatures.

3.3. Research Hypotheses

3.3.1. Primary Hypotheses:

1. There will be good test-retest reliability for the sustained cold response test (ADI-sustained cold), topical menthol cold response test (ADI-topical menthol) and cold pain threshold (CPT) temperature.
2. There will be positive correlations between each cold response test:
 - a. Sustained cold response (ADI-sustained cold);
 - b. Topical menthol cold response (ADI-topical menthol);
 - c. CPT temperature
3. Participants in high sustained cold and menthol cold groups will exhibit higher CPT temperatures.

3.4. Methods

3.4.1. Participants

The study was conducted in the School of Physiotherapy and Exercise Science at Curtin University in Perth, Western Australia. A total of 40 participants were recruited voluntarily from the community.

Volunteers with current pain or a history of lateral epicondylalgia and/or neck pain with radiation to the forearm were excluded due to potential influence on thermal stimuli. Volunteers with limited understanding of English were also excluded. Inclusion and exclusion criteria were as table 3.1.

Table 3.1: Inclusion / Exclusion criteria

Inclusion Criteria	<ul style="list-style-type: none">• Aged between 18 and 65 years old• No current pain• Good comprehension of spoken and written English language
Exclusion Criteria	<ul style="list-style-type: none">• History of lateral epicondylalgia / tennis elbow• History of neck pain with radiation to forearm• History of other chronic pain condition• Altered / loss of sensation at the volar forearm test site

All participants provided written informed consent before participating in the study. Ethical approval was granted by Curtin University Human Research Ethics Committee (Approval Number PT0188).

3.4.2. Study Design and Procedure

This study utilized a test-retest design. Participants attended 2 sessions within a single week, each session separated by a washout period of at least 24 hours. On each test occasion the same protocol was followed. A test site (2 x 3 cm) on each volar forearm approximately mid-way between the wrist and elbow creases was used. Cold detection and cold pain thresholds (CDT

and CPT) were first tested at this site on both arms. Sustained cold was then tested on a randomly allocated forearm. Randomization was done using a random number generator application on a smart phone. Participants allocated an odd number started the test on the right forearm, those with an even number started the test on the left forearm. Topical menthol cold was then tested on the other forearm. Sustained cold was always tested first to ensure that any lingering sensory effects of menthol did not influence the thermode cold response. The same protocol was used on each occasion. The same test site and same order of testing was used on both test occasions: sustained cold on one forearm, Topical menthol cold tested on the other forearm.

3.4.3. Outcome Measures

Quantitative Sensory Tests:

All quantitative sensory testing was conducted with the participant sitting in an arm chair, with their arms placed on a table. All instructions were standardized.

1. **Cold Detection and Pain Thresholds** was measured using a peltier thermode (Medoc, Israel). The minimum temperature was set at 0°C. A 30x30mm contact probe was attached to the test site with a strap and the participant was given several minutes to adapt to the baseline temperature of 32°C. When the device was activated, the thermode temperature fell at a rate of 1°C/sec. This rate of temperature change has been shown to reduce intra-individual variation (Palmer et al., 2000). The participant was given a control switch and instructed to press the switch when they perceived the relevant sensation (i.e. if it was a cold detection threshold test, the participant was instructed to depress the switch once they detected cold). The cold detection threshold was always tested before the cold pain threshold to minimise sensitization of receptors by the noxious input. For each threshold, 1 practice trial was followed by 3 measurements, with the mean calculated for analysis. Each stimulus was separated by a randomised 3 to 6 second interval. See Section 2.4.3. for details on the reliability of the thermal detection and pain thresholds.



Figure 3.1

Photograph of the Medoc TSA II system with peltier thermode.

2. **Sustained Cold Response** was tested using a newly developed wearable peltier thermode (Dhama, India). This battery powered device creates a cool temperature through standard thermo-electric methods but has been designed to be worn on the forearm. The device comprises a 2x3cm thermode plate that is embedded in a rigid arm wrap. The wrap is kept damp in order to facilitate dissipation of the heat produced by the cooling process. The thermode can be set to several different specific temperatures using touch controls and maintains this temperature for up to 5 minutes (Figure 3.1).



Figure 3.2

Photograph of the Dhama thermode system showing the control unit and the pad for application to the arm.

For this study, the Dhama thermode was set to 12°C. This temperature was selected as being warmer than the average normal CPT of 7-10°C but sufficiently cold to elicit a response in all participants. Before application to each participant, the external surface of the thermode was sprayed with water to allow for heat evaporation, and the thermode plate temperature checked using a thermistor. It was then applied to the participant's volar forearm for 5 minutes, using the timer on the ADI Apple iPad application (see below). On completion of the 5-minute test it was removed from the patient's forearm before being turned off.

Response to the sustained cold stimulus was measured using the ADI, delivered via an Apple iPad application (Moss, 2013). The ADI combines measures of perceived sensation intensity with a measure of sensory quality. Intensity of cold, heat, unpleasantness and pain sensation is assessed throughout the thermode application using the 4 calibrated 100mm VAS sliding scales shown on the iPad touch screen

(Figure 3.2). A pre-determined algorithm calculates an ADI-VAS index score from these 4 scales.

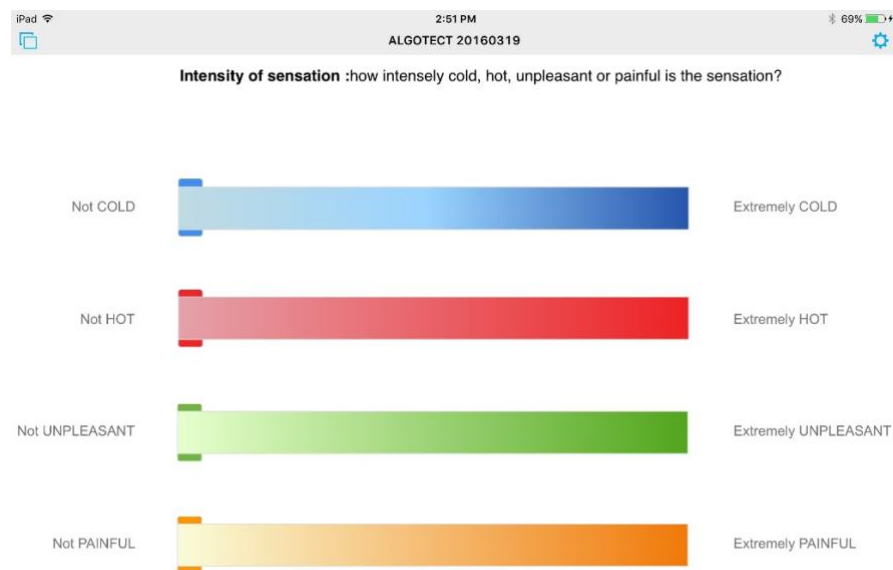


Figure 3.3

Screenshot of the 4 calibrated 100mm VAS sliding scales to assess cold, heat, unpleasantness and pain.

Participants are also asked to select words that best describe the quality of the sensation experienced during the 5-minute thermode application from a set of descriptors based on the key sensory elements of the McGill Pain Questionnaire descriptor list (Melzack, 1975) (Figure 3.3). An algorithm calculates a descriptor index value based on words selected.

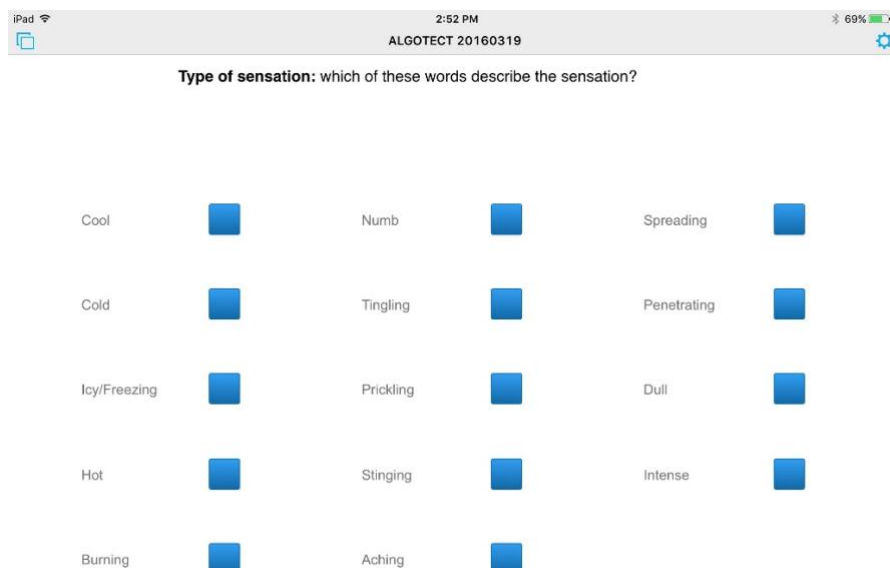


Figure 3.4

Screenshot of the ADI descriptors showing the range of sensory descriptors that can be selected.

Using a specially-designed timed iPad Application, ratings for either intensity or quality were taken every 30-seconds in alternating fashion during the 5-minute thermode application. A previously developed algorithm was used to calculate a total ADI score based on the combined intensity and quality responses (Moss, 2013). As well as calculating a total sustained cold ADI score (min 0, max 9), a subscore for combined VAS intensity for cold, heat, unpleasantness and pain (max score 4) and a subscore for sensation quality (mean word score (MWS), max score 5) were also calculated, using the method described by Moss (2013).

3. **Topical Menthol Cold** was tested by applying for 15 minutes, a previously tested (Moss, 2013) gel formulation of 20% menthol. Before application of the menthol gel formulation, the test area was marked and gently cleaned with hypoallergenic soap and tepid water. 2ml of menthol gel was applied to the test site using a 5ml syringe. A Tegaderm© dressing was immediately placed over the gel to minimize evaporation, and the gel then gently spread through the dressing so

that it exactly filled the 2x3cm dressing window. When the 15-minute application ended, the Tegaderm® dressing was removed and the menthol gel cleaned from the skin using hypoallergenic soap and tepid water. The skin was gently dried with a paper towel.

Response to the topical menthol cold was measured using the ADI, delivered via the same Apple iPad application, although using a 15-minute version. Once the menthol and dressing had been applied, the 15-minute timer was started. Every minute, participants were asked either to rate the intensity of cold, heat, unpleasantness or pain they were feeling, using the 4 calibrated 100mm VAS sliding scales or to select descriptors which best describe the quality of sensation they were feeling. The same algorithm calculated a topical menthol cold ADI score based on the combined intensity and quality responses (min 0, max 9). Subscores for intensity ratings (max 4) and for sensation quality (MWS, max 5) were also calculated (Moss, 2013).

3.4.4. Power Analysis

Using data from a previous CPT study (Moss et al., 2011) it was calculated that a sample size of between 40 and 50 participants would provide 80% power ($\alpha=0.05$) to assess test-retest reliability between the 2 test occasions. There are no published data regarding the test-retest reliability for either topical menthol cold or sustained cold tests. Data collected during the present study will help to inform power analyses for future clinical studies.

3.4.5. Data Analysis

Statistical analysis was completed using IBM SPSS Statistics version 22, with alpha set at 0.05. Data were tested for normality using normal distribution curves and Shapiro-Wilks tests. For threshold testing, CDT was normally distributed but CPT showed its usual bi-modal distribution. Sustained cold ADI values were normally distributed (Shapiro-Wilks 0.974, $p=0.433$) although topical menthol cold ADI values were not (Shapiro-Wilks 0.335, $p<0.001$). Due to the mixed normality results, non-parametric tests were used where appropriate. Table 3.2 shows the statistical tests for each hypotheses.

Table 3.2: Hypotheses and Statistical Test Used

Hypotheses and Related Data	Statistical Analysis
1. Test-retest reliability for ADI-sustained cold, ADI-topical menthol and CPT temperature.	Intra-Class Correlation Coefficients (ICC) (2-way mixed, consistency)
2. Correlations between each cold response test.	
i. ADI-sustained cold	Spearman's Correlation Coefficients (2-tailed)
ii. ADI-topical menthol	
iii. CPT temperature	
3. Ability to differentiate abnormal CPT response to cold using:	Hierarchical cluster analysis
i. Sustained cold response	Chi-squared analysis
ii. Topical menthol cold response	Mann Whitney U-Test

Data analysis for primary hypothesis 3 (Ability of sustained and topical menthol cold responses to differentiate an abnormal CPT response to cold) was more complex and evaluated using several different methods.

Hierarchical cluster analysis was first used to investigate groupings for topical menthol and sustained cold ADI total scores. Optimal cut-offs between groups were then calculated. Chi-squared analysis was used to compare membership of high and low sustained cold and topical menthol cold groups with high and low CPT groups ($<15^{\circ}\text{C}$) (Allchorne et al., 2005; Davis & Pope, 2002; Story et al., 2003) and Mann-Whitney-U tests run to investigate differences in mean CPT values between high and low cold response groups.

3.5. Results

3.5.1. Participant Demographics

A total of forty-two participants (eighteen male and twenty-four female; mean age 30.1 ± 8.2 , range 18-49) took part in the study. There were no drop outs, all forty-two participants completed the study.

3.5.2. Primary Hypothesis 1:

There will be good test-retest reliability for Algotect Descriptor Index (ADI)-sustained cold, ADI-topical menthol and CPT temperature.

- **Sustained Cold**

The ADI-sustained cold test demonstrated excellent test-retest reliability for the 2 subscores (VAS intensity (ICC: 0.821; 95% CI:0.691-0.900) and MWS (ICC_{3,1}: 0.794; 95%CI: 0.648-0.884)) and the total score (ICC: 0.855; 95% CI: 0.713-0.952) (Table 3.3).

- **Topical Menthol**

The ADI-topical menthol test demonstrated excellent test-retest reliability for the 2 subscores (VAS intensity (ICC: 0.879; 95% CI:0.776-0.935) and MWS (ICC: 0.834; 95%CI: 0.711-0.907)) and the total score (ICC_{3,1}: 0.851; 95% CI: 0.739-0.917) (Table 3.3).

- **Cold Pain Threshold**

The CPT temperature demonstrated excellent test-retest reliability (ICC_{3,1}: 0.941; 95% CI: 0.892-0.968) (Table 3.3).

Table 3.3 Test-retest reliability over 2 occasions separated by at least 24 hours – Intra-Class Correlation Coefficient (ICC_{3,1}), showing 95% Confidence Intervals (CI)

	ICC _{3,1} * r=	95% CI
Sustained cold		
• VAS intensity	0.821	0.691-0.900
• MWS	0.794	0.648-0.884
• Total ADI score	0.855	0.713-0.952
Topical menthol cold		
• VAS intensity	0.879	0.776-0.935
• MWS	0.834	0.711-0.907
• Total ADI score	0.851	0.739-0.917
Cold Pain Threshold		
• CPT temperature (°C)	0.941	0.892-0.968

* All ICCs $p < 0.001$

3.5.3. Primary Hypotheses 2:

There will be positive correlations between each cold response test:

- a. Sustained cold response (ADI-sustained cold);
- b. Topical menthol cold response (ADI-topical menthol);
- c. Cold pain threshold (CPT) temperature.

- **ADI-sustained cold and ADI-topical menthol**

There was a moderate positive strength of association between the ADI-sustained cold test and the ADI-topical menthol test (VAS intensity ($r=0.458$, $p=0.002$), MWS ($r=0.417$, $p=0.006$) and ADI total ($r=0.500$, $p=0.001$)) (Table 3.4).

Table 3.4: Spearman's correlation coefficient (ADI-sustained cold and ADI-topical menthol)

		ADI-topical menthol		
		VAS intensity	MWS	ADI total
ADI-sustained cold				
• VAS intensity	r=	0.458	-0.131	0.334
	p=	0.002*	0.408	0.031*
• MWS	r=	0.453	0.417	0.545
	p=	0.003*	0.006*	0.000*
• ADI total	r=	0.547	0.098	0.500
	p=	0.000*	0.537	0.001*

* Indicates statistical significance at $p \leq 0.05$

- **ADI-sustained cold and CPT**

There was a moderate positive strength of association between ADI-sustained cold total score and CPT ($r=0.355$, $p=0.021$). No significant associations were established between the VAS intensity and MWS sub scores (Table 3.5).

Table 3.5: Spearman's correlation coefficient (ADI-sustained cold and CPT)

	CPT	
	r	p
ADI-sustained cold		
• VAS intensity	0.269	0.085
• MWS	0.283	0.069
• ADI total	0.355	0.021*

* Indicates statistical significance at $p \leq 0.05$

• ADI-topical menthol and CPT

There was a moderate positive strength of association between ADI-topical menthol and CPT (MWS subscore ($r=0.389$, $p=0.009$) and total score ($r=0.413$, $p=0.007$)) (Table 3.6).

Table 3.6: Spearman's correlation coefficient (ADI-topical menthol and CPT)

	CPT	
	r	p
ADI-topical menthol		
• VAS intensity	0.293	0.059
• MWS	0.398	0.009*
• ADI total	0.413	0.007*

* Indicates statistical significance at $p \leq 0.05$

3.5.4. Primary Hypothesis 3:

Participants in the high sustained cold response group and the high menthol cold response group will exhibit higher CPT temperatures.

Hierarchical cluster analyses were used to identify clear participant groups for sustained cold total ADI and for topical menthol cold total ADI values.

Group sizes and cut-off values were then calculated.

For ADI-sustained cold total values, two groups could be identified with 38 participants in the low ADI group, 4 in the high ADI group and a cut-off value

of 6.07. Additional descriptive values for each group are shown in Table 3.7 below.

Table 3.7: Descriptive group values for ADI-sustained cold total

	Maximum	Minimum	Median	Mean	SD*
Group 1 (n=38)	5.14	2.14	3.92	3.80	0.878
Group 2 (n=4)	9.06	5.60	7.00	6.20	0.503

* SD: Standard Deviation

For ADI-topical menthol total values, two groups were also identified with 38 participants in the low ADI group and 4 in the high ADI group (Table 3.8). The cut-off for the ADI-topical menthol score was 5.10.

Table 3.8: Descriptive group values for ADI-topical menthol total

	Maximum	Minimum	Median	Mean	SD*
Group 1 (n=38)	4.08	1.50	3.0	2.94	0.135
Group 2 (n=4)	6.22	4.50	5.0	5.09	0.166

* SD: Standard Deviation

Mann-Whitney U-tests were then used to evaluate whether there was a difference in conventional cold response test values (CPT temperature) between sustained cold or topical menthol cold groups. However, no significant difference in CPT value was found between high or low score groups for either sustained cold or menthol cold tests, although there was a trend towards significance for difference in CPT values between menthol cold high and low value groups (Table 3.9).

Table 3.9: Differences in CPT temperature between high and low ADI total groups for sustained cold and topical menthol

	Mean (SD) CPT value (°C)	Mann Whitney U-Test
Sustained cold		
• Low ADI total group (n=38)	8.03 (9.07)	p=0.468
• High ADI total group (n=4)	9.83 (9.66)	
Topical menthol		
• Low ADI total group (n=38)	7.39 (8.54)	p=0.067
• High ADI total group (n=4)	16.40 (9.56)	

Summary of Results

Hypotheses	Accepted/Rejected
1. There will be good test-retest reliability for sustained cold response test (ADI-sustained cold), topical menthol cold response test (ADI-topical menthol) and cold pain threshold (CPT) temperature.	Accepted
2. There will be positive correlations between each cold response test: i. Sustained cold response (ADI-sustained cold) ii. Topical menthol cold response (ADI-topical menthol) iii. Cold pain threshold (CPT) temperature	Accepted
3. Participants in high sustained cold and menthol cold groups will exhibit higher CPT temperatures.	Rejected

3.6. Discussion

This study aimed to assess the reliability and validity of two alternative simple methods of testing cold response, as compared to the conventional cold pain threshold testing.

The presence of cold hyperalgesia has been documented in a range of musculoskeletal pain conditions (Coombes et al., 2012; Moss et al., 2016; Park et al., 2010; Steinmetz & Jull, 2013; Tampin et al., 2012; Wright et al., 2017), and has been shown to be a consistent predictor of poor outcomes in whiplash injury and lateral epicondylalgia (Coombes et al., 2015; Sterling et al., 2005). The 'gold standard' of assessing cold hyperalgesia is by using a computer-controlled peltier thermode, however the cost and maintenance of these devices present a major hurdle for its widespread use clinically.

Test-Retest Reliability

The finding of excellent test-retest reliability of the standard test of cold pain threshold supports the current evidence in the scientific literature (Geber et al., 2011; Heldestad et al., 2010; Moss et al., 2016; Pigg et al., 2010; Wasner & Brock, 2008). The present study has also demonstrated the excellent test-retest reliability of two alternative ways of testing cold response. As the sustained cold response and topical menthol response tests are newly developed tests, there are no current evidence available on the reliability and validity of these tests with which to compare these reliability data. The data collected from this study on the reliability and validity of these two new measures of cold response will inform power analyses for future clinical studies.

Correlations and Validity

This study showed that there were moderate to weak correlations between CPT values and the new tests of cold response sustained cold and topical menthol cold. Although not causative, this suggests that the newly developed tests of cold response are evaluating a similar phenomenon to the gold standard CPT test, despite using a very different response measurement. Hence, it can be assumed that the two new cold response tests have face

and content validity in the measurement of cold hyperalgesia. Further studies are needed to confirm these findings.

Differentiation of abnormal cold responses

Sustained cold response and topical menthol tests were not however able to clearly differentiate participants with abnormally high responses to standard CPT cold testing. Cluster analysis showed a clear delineation between high and low scores for both the sustained cold and topical menthol cold ADI scores, but there was no significant difference in CPT values between groups for either new cold test. It may be noted that there was a visible difference and trend towards statistical significance in CPT values between topical menthol cold high and low score groups, with the mean value for the high topical menthol cold group being $>15^{\circ}\text{C}$, a previously suggested cut-off for cold hyperalgesia (Allchorne et al., 2005; Davis & Pope, 2002; Story et al., 2003). This suggests that a future study, with greater participant numbers, may demonstrate a clearer association between topical menthol cold response with ADI and CPT. Such a finding would indicate the usefulness of a simple clinical test for cold hyperalgesia based on intensity and quality response to topically-applied menthol.

Study Limitations

The limitations of this study must be acknowledged. These include a small sample size, relatively young age of the participants (mean age of 30.14 years) and the population tested are all healthy participants. Due to the small sample size, the topical menthol response test was not able to significantly differentiate an abnormal CPT response to cold. However, we envisage that with a larger sample size, the topical menthol response test will be able to significantly differentiate an abnormal CPT response to cold. Due to the limitations of young age and a healthy population, we are unable to definitively conclude that positive correlations found in this study can be generalized to an elderly or diseased population. Moving forward, this study should be expanded to include a larger sample, a wider range of ages and disease specific populations (e.g. knee osteoarthritis, neuropathic pain).

Implications

The results of this study have demonstrated the reliability and validity (face and content) of the two alternative simple methods of testing cold response, as compared to the conventional cold pain testing. This means that clinicians now have alternative ways of assessing cold hyperalgesia quickly and accurately, without using the bulky and costly computer-controlled peltier thermode devices.

3.7. Conclusion

In conclusion, this study has proven the reliability and validity of both the sustained cold and topical menthol cold tests. Consequently, these two new tests appear to offer clinicians an appropriate, quick, low-cost and simple way to test for cold hyperalgesia in a young and healthy population. Further studies are needed to demonstrate that the results of this study can be replicated in an elderly or diseased population. The sustained cold response test was chosen as a quantitative sensory test in the next study (Study 3) due to its ease of use and shorter application time.

Chapter 4

Study 3

Evaluation of predictors for persistent pain post-Total Knee Replacement

4.1. Abstract

Background and Aims

Persistent pain following TKR may reflect new pain resulting from the surgical intervention or may reflect lack of success in resolving pre-existing, 'old' pain. This study aimed to investigate whether persistent pain at 6 months following TKR surgery can be predicted by measures of pain, function, psychological distress or quantitative sensory testing (QST) at pre-operative baseline and/or at 3 months post-surgery.

Method

A prospective cohort design was used. A total of ninety-two participants who underwent TKR within Royal Perth Hospital, Fremantle Hospital and Health Service and at St John Of God Subiaco and Murdoch Hospitals were assessed pre-operatively and at 3 months post-operatively using a range of self-report, QST and intra-operative measures, all of which have been proposed as potential predictors of persistent post-operative pain. At the time of submission of this thesis, seventy-four participants had reached the 3 months post-surgery time point. Out of these seventy-four participants, sixty had reached the 6 months post-surgery time point.

At 3 months post-TKR, participants were divided into 'no to low pain' and 'moderate to severe pain' groups, based on their pain levels (Pain Average score from the PainDETECT questionnaire).

At 6 months post-TKR, participants were divided into 'good outcome' and 'poor outcome' groups, based on Knee Society Score.

Differences in the abovementioned range of measures were investigated between the groups at 3 and 6 months post-TKR. Logistic regression was then used to determine the predictive value of the measures in determining persistent pain post-TKR.

Results

Group differences

At 3 and 6 months post-TKR, there were significant group differences in a range of pre-operative physical measures and self-reported outcomes.

At 6 months post-TKR, there were significant group differences in a range of 3 months post-surgery self-reported outcomes.

Predictors of post-TKR pain.

Pre-operative predictors of higher pain levels at 3 months post-TKR surgery were vibration detection threshold (VDT) at the elbow (odds ratio (OR)=1.38, $p=0.002$) and PainDETECT score (OR=1.16, $p=0.041$).

Pre-operative predictors of membership of the poor outcome group at 6 months post-TKR were VDT average of all sites (OR=1.09, $p<0.001$) and WOMAC Pain score (OR=1.5, $p=0.003$).

3 months post-TKR predictors of membership into the poor outcome group at 6 months post-TKR were pain catastrophising (OR=1.19, $p=0.033$) and pain intensity (OR=5.42, $p=0.01$).

Conclusion

Individuals with higher pain levels at 3 months post-TKR surgery, pre-operatively exhibited widespread sensory changes, poorer function, higher levels of neuropathic-type pain, pain catastrophising, lower health status, higher WOMAC scores, psychological distress and reduced sleep quality.

Individuals with poor outcomes at 6 months post-TKR surgery, preoperatively exhibited widespread sensory changes, poorer function, higher levels of neuropathic-type pain, pain catastrophising, lower health status, more co-morbid conditions, higher WOMAC scores and increased psychological distress.

Individuals with poor outcomes at 6 months post-TKR surgery, at the 3 months post-TKR assessment had higher levels of neuropathic-type pain, increased pain catastrophising, lower health status, more co-morbid conditions, higher WOMAC scores, increased psychological distress and poorer sleep quality.

4.2. Overview, Aims and Objectives

TKR surgery has increased by 92.4% since 2003 (AOANJRR, 2013). Persistent pain reduces function and quality of life for between 13% and 44% of patients post-TKR surgery (Baker et al., 2007; Brander et al., 2003; Puolakka et al., 2010; Wylde et al., 2007; Wylde et al., 2011). Based on the number (AOANJRR, 2013) and cost (Independent Hospital Pricing Authority, 2013) of TKR operations in Australia in 2012, and the rates of persistent post-TKR pain reported in the literature (Baker et al., 2007; Beswick et al., 2012; Brander et al., 2003; Puolakka et al., 2010; Wylde et al., 2007; Wylde et al., 2011), it can be postulated that the cost of the failed surgery alone ranges from \$102 million - \$128 million (13%) to \$347 million - \$436 million (44%). Yet the interactions between factors contributing to this pain are still poorly understood and have not yet been comprehensively evaluated in a longitudinal study. Persistent post-surgical pain is often a combination of pre-existing unresolved pain and newly acquired pain post-surgery (Kehlet et al., 2006; Perkins & Kehlet, 2000; Suokas et al., 2012; Vilardo & Shah, 2011; Wylde et al., 2013). Therefore, greater clarity is needed about the relative roles of these 2 issues in the development of persistent post-surgical pain. This study used a wide range of peri-operative data from self-report, QST, and medical notes to evaluate predictors of pain that persists up to 6 months post-TKR surgery. It is hoped that the findings from this study will assist in the pre-operative assessment and post-operative pain management of patients undergoing TKR.

The objectives of this study were:

1. To investigate whether there is a difference at pre-operative baseline in QST measures, pain report, functional level and health status between participants categorized as having no to low pain (<4 in NRS pain) versus moderate to severe pain (≥ 4 in NRS pain) at 3 months following TKR surgery.
2. To investigate whether there is a difference at pre-operative baseline and at 3 months post-surgery in QST measures, pain report, functional level and health status between participants categorized as showing 'poor'

versus 'good' outcomes (based on Knee Society Score) at 6 months following TKR surgery.

4.3. Research Hypotheses

4.3.1. Primary Hypotheses:

1. There will be a difference at pre-operative baseline in QST measures, pain report, functional level, health status, psychological distress and sleep quality between participants categorized as having no to low pain (<4 in NRS pain) versus moderate to severe pain (≥4 in NRS pain) at 3 months following TKR surgery.
2. There will be a difference at pre-operative baseline and at 3 months post-surgery in QST measures, pain report, functional level, health status, psychological distress and sleep quality between participants categorized as showing 'poor' versus 'good' outcomes (based on Knee Society Score) at 6 months following TKR surgery.

4.3.2. Secondary Hypotheses:

1. Pre-operative baseline measures (which may include cold pain threshold (CPT), pressure pain threshold (PPT), PainDETECT score, WOMAC score, psychological distress or sleep quality index score) will predict moderate to severe pain levels at 3 months post-TKR surgery.
2. Pre-operative baseline measures (which may include cold pain threshold (CPT), pressure pain threshold (PPT), PainDETECT score, WOMAC score, psychological distress or sleep quality index score) will predict 'poor' outcome at 6 months post-TKR surgery.
3. 3 months post-TKR surgery measures (which may include CPT, PPT, PainDETECT score, surgical approach, immediate post-operative pain intensity or pain catastrophising) will predict 'poor' outcome at 6 months post-TKR surgery.
4. Baseline CPT values will predict membership into the 'poor' outcome group at 6 months with good sensitivity and specificity.
5. Baseline PainDETECT scores will predict membership into the 'poor' outcome group at 6 months with good sensitivity and specificity.

4.4. Methods

4.4.1. Participants

The study was conducted in Royal Perth Hospital (RPH), Fremantle Hospital and Health Service (FHHS), and St John of God (SJOG) Subiaco and Murdoch Hospitals in Perth, Western Australia.

Inclusion/exclusion criteria are listed below. All individuals listed on the surgical lists were contacted, initially by providing written information by post and then following up with a phone call. No RPH, FHHS, SJOG Subiaco and Murdoch Hospitals' staff were involved in direct recruitment of participants to the present study, to avoid power and ethical issues.

Volunteers with numbness around the knee, haemophilia or previous history of stroke were excluded from the study because those factors can possibly influence the perception of thermal and pressure stimuli. Volunteers with limited understanding of English were also excluded because of the need to complete questionnaires in English. Inclusion and exclusion criteria were as in Table 4.1.

Table 4.1: Inclusion / Exclusion criteria

Inclusion Criteria	<ul style="list-style-type: none">• Above 50 years old• Undergoing primary uni-lateral TKR because of OA• Good comprehension of English language
Exclusion Criteria	<ul style="list-style-type: none">• Recent surgery (<6 months) in the contralateral knee and/or ipsilateral elbow• Any cognitive impairment• Any neurological conditions (i.e. previous stroke)• Numbness around the knee and/or ipsilateral elbow• Haemophilia

All participants were advised to continue with their usual medications prior to attending the assessment session.

All participants provided written informed consent before participating in the study. Ethical approval was granted by Royal Perth Hospital Medical Research Ethics Committee (Approval Number: REG 14-141), Curtin University Human Research Ethics Committee (Approval Number: HR 220/2014) and St John of God Health Care Human Research Ethics Committee (Approval Number: 926).

4.4.2. Study Design and Procedure

This study utilized a prospective cohort method, in which patients undergoing TKR within RPH, FHHS and at SJOG Subiaco and Murdoch Hospitals were assessed pre-operatively and at 3 months post-operatively using a range of self-report, QST and intra-operative measures, all of which have been proposed as potential predictors of persistent post-operative pain (Elson & Brenkel, 2006; Kehlet et al., 2006; Macrae & Davies, 1999; Vilardo & Shah, 2011). The timeline for assessments and range of self-report and physical tests utilized are as shown in Appendix 2.

4.4.3. Outcome Measures

Self-Reported Measures:

All participants completed a paper version of all the questionnaires on the day of their research assessment. The questionnaires were as stated below.

Disease-specific

1. Western Ontario and McMaster Universities Osteoarthritis Index

(WOMAC) is a disease-specific self-report measure designed for standardised reporting of individuals with knee or hip osteoarthritis (Bellamy, 1989). It consists of 24 items divided over 3 subscales: pain, joint stiffness and physical function. The WOMAC questionnaire (Likert version 3.1) was administered with the pain subscale last, as it has been hypothesized that participants' responses to the pain questions may bias the responses to some of the questions in the physical function subscale (Pua et al., 2009; Terwee et al., 2006). See Section 2.4.3. for details on the reliability of the WOMAC questionnaire.

Health and Well-being

2. **Short-Form 36 Health Survey (SF-36)** was used to measure functional health and well-being. It contains 8 health domains (Physical functioning (PF), Role limitations due to physical functioning (RP), Bodily pain (BP), General health perceptions (GH), Vitality (VT), Social functioning (SF), Role limitations due to emotional problems (RE) and Mental health (MH)) and 2 component summary measures (Physical component summary (PCS) and Mental component summary (MCS)) (McHorney et al., 1994). The SF-36 questionnaire has demonstrated good discriminant validity and adequate reliability (Cronbach's Alpha: 0.75 to 0.91) (Kosinski et al., 1999; Kosinski et al., 1999; Mchorney et al., 1994).

Comorbid Conditions

3. **Self-Administered Comorbidity Questionnaire (SCQ)** is a 15-item self-report questionnaire that assesses for the presence of 12 medical conditions for people with no prior medical knowledge. There are an additional 3 optional questions regarding any other medical conditions. See Section 2.4.3. for details on the reliability of the SCQ questionnaire.

Pain

4. **PainDETECT** is a self-report screening tool to identify neuropathic pain components (Freynhagen & Baron, 2006). It consists of 9 items over 3 categories: pain quality, pain pattern and pain radiation. It has also been used in a number of studies looking at the presence of neuropathic pain components in other musculoskeletal conditions including osteoarthritis (Gwilym et al., 2011; Jespersen et al., 2010; Moss et al., 2017; Ohtori et al., 2012; Shigemura et al., 2011). See Section 2.4.3. for details on the reliability of the PainDETECT questionnaire.
5. **Pain Quality Assessment Scale (PQAS)** is used to provide additional data regarding the dimensions of spontaneous pain experienced by participants (Victor et al., 2008). The PQAS was developed by adding additional items to the 10-item Neuropathic Pain Scale (NPS) (Jensen, 2006). The PQAS has been reported to provide

more comprehensive information about pain quality than alternative single dimensional pain scales (Jensen et al., 2012). It has also been shown to have validity for assessing treatment-related changes in pain quality and spatial characteristics (Jensen et al., 2006). Factor analysis of the PQAS questionnaire revealed 3 clear pain quality domains: (1) Paroxysmal pain, (2) Superficial pain and (3) Deep pain (Victor et al., 2008). See Section 2.4.3. for details on the reliability of the PQAS questionnaire.

6. **Pain Catastrophising Scale (PCS)** is a self-report questionnaire describing thoughts and feelings that individuals might experience when in pain. It has 13 items over 3 subscales: rumination, magnification and helplessness (Sullivan et al., 1995). The PCS demonstrates adequate reliability (Cronbach's Alpha: 0.87) (Sullivan et al., 1995); (Cronbach's Alpha: 0.91 for rumination subscale; 0.75 for magnification subscale; 0.87 for helplessness subscale; 0.93 for total PCS) (Osman et al., 1997), and good criterion-related, concurrent and discriminant validity (Osman et al., 2000).
7. **Numeric Rating Scale (NRS)** is a single 11-point numeric scale for rating pain intensity. It has also been shown to have high test-retest reliability (Pearson's r : 0.95 to 0.96) (Ferraz et al., 1990), and high construct validity (0.86 to 0.95) (Downie et al., 1978; Ferraz et al., 1990).

Psychological Distress

8. **Patient Health Questionnaire-8 (PHQ-8)** is an 8-item self-report questionnaire screening for severity of depression. The PHQ-8 is used in place of the PHQ-9 in this study, as the PHQ-8 can be done via self-administration (Kroenke & Spitzer, 2002). PHQ-9 has demonstrated good reliability (Cronbach's Alpha: 0.89) (Kroenke & Spitzer, 2002) and has been found to have a sensitivity of 77% and specificity of 94% for detection of a depressive disorder (Wittkamp et al., 2007). The PHQ-8 and PHQ-9 have been shown to have similar abilities in predicting any depressive disorder, as well as having similar sensitivity, specificity and positive prediction values (Kroenke & Spitzer, 2002).

Sleep Quality

9. **Pittsburgh Sleep Quality Index (PSQI)** is a 19-item self-report questionnaire used to measure sleep quality and disturbances for the past one month and to discriminate between 'good' and 'poor' sleepers (Buysse et al., 1988). It contains 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications and daytime dysfunction. The PSQI has been demonstrated to have a high degree of internal homogeneity (Cronbach's Alpha: 0.83), acceptable test-retest reliability (Pearson's r : 0.46 to 0.85), validity, and high sensitivity (89.6%) and specificity (86.5%) in distinguishing good and poor sleepers (Buysse et al., 1988).

Physical / Sensory measures:

Physical Measures

1. **Range of Motion (ROM)** of the knee (flexion and extension) was measured using a handheld goniometer. Both active and passive ROM were measured. The standard handheld goniometer has been shown to be a reliable instrument for measurement of active ROM (ICC: 0.95 for flexion, ICC: 0.85 for extension) and passive ROM (intra-tester reliability (ICC: 0.99 for flexion, ICC: 0.98 for extension) and inter-tester reliability (ICC: 0.90 for flexion, ICC: 0.86 for extension)) of the knee (Clapper & Wolf, 1998; Watkins et al., 1991). The position for measurement of ROM was standardised to the supine position. 3 measurements were taken, with the mean calculated for analysis.
2. **Aggregated Locomotor Function Score (ALF)** is a measure of observed locomotor function. It consists of 3 components: 8 metre walk time, stair ascent and descent time and transferring time (McCarthy & Oldham, 2004). 3 repetitions of the 8 metre walk were undertaken, with the mean calculated for analysis.
 - 4 repetitions of the stair ascent and descent were undertaken, with the mean calculated for analysis.

- 3 repetitions of the transfer were undertaken, with the mean calculated for analysis.

The total time (sum of the mean time for each section) was used for analysis and comparison with previous studies.

The ALF has been shown to have excellent intra-tester reliability (ICC_{2,k}: 0.99; 95% CI: 0.98-0.99), low standard error of measurement (0.86 s) and low smallest detectable difference (9.5%) values (McCarthy & Oldham, 2004).

3. **Knee Extensor Strength** was measured using a handheld dynamometer, with the participants in supine position, and the knee positioned at 35° of knee flexion. Participants were put through an isometric make test. The isometric make test is easier to perform and produces more reliable results (Smidt & Rogers, 1982). Martin et al. (2006) showed that testing of quadriceps strength in this position with handheld dynamometry shows a strong positive correlation (Pearson's r : 0.91) and agreement with Biodex dynamometry values. 3 measurements were taken, with the mean calculated for analysis.

Quantitative Sensory Tests:

Test sites:

Apart from the sustained cold response test, all other quantitative sensory tests were performed at the medial joint line of both knees and over the ipsilateral extensor carpi radialis brevis (ECRB) muscle in the upper limb. For sustained cold response, the test site was at the ipsilateral ECRB. The ECRB muscle has been used previously in other quantitative sensory test studies (Slater et al., 2003; Slater et al., 2005). The site was located by using the standardized method as described by Riek et al. (2000). The quantitative sensory testing was conducted with the participant lying in a relaxed position on a plinth. With the exception of the sustained cold response test, the method of limits approach was used for all of the quantitative sensory tests stated below.

4. **Pressure Pain Threshold (PPT)** was measured using an electronic, digital algometer (Somedic, Sweden) with a 1cm² round rubber tip at

the end connected to a pressure transducer within the handle of the unit. The algometer was applied at a 90° angle to the skin at a constant rate of 40 kPa/sec. The subject was given a control switch and instructed to press the switch when the sensation changed from pressure to pain, at which time the test was terminated. 1 practice trial was followed by 3 measurements, with the mean calculated for analysis (Lacourt et al., 2012; Persson et al., 2004). See Section 2.4.3. for details on the reliability of PPT.

5. **Cold/Heat Detection and Pain Thresholds** were measured using a peltier thermode (Medoc, Israel). The minimum temperature was set at 0°C, and the maximum temperature set at 50°C. A 30x30mm contact probe was attached to the test site with a strap and the participant was given several minutes to adapt to the baseline temperature of 32°C. When the device was activated, the thermode temperature rose or fell at a rate of 1°C/sec. This rate of temperature change has been shown to reduce intra-individual variation (Palmer et al., 2000). The subject was given a control switch and instructed to press the switch when they perceived the relevant sensation (i.e. if it was a heat detection threshold test, the participant was instructed to depress the switch once they detected heat). The respective thermal detection thresholds were always tested before the thermal pain thresholds to minimise sensitization of receptors by the noxious input. The thresholds were tested in the order of **cold detection threshold (CDT), cold pain threshold (CPT), heat detection threshold (HDT) and heat pain threshold (HPT)**. For each threshold, 1 practice trial was followed by 3 measurements, with the mean calculated for analysis. Each stimulus was separated by a randomised 3 to 6 second interval. See Section 2.4.3. for details on the reliability of the thermal detection and pain thresholds.
6. **Vibration Detection Threshold (VDT)** was assessed using an electronic vibrometer (Medoc, Israel), which has a threshold range of 0-130µm, at a rate of 0.5µm/sec. The participant was given a control switch and instructed to press the switch when they first become aware of the stimulus. VDT has demonstrated excellent test-retest

reliability (ICC: 0.86; 95% CI: 0.79-0.91) in normals (Felix & Widerström-Noga, 2009). 1 practice trial was followed by 3 measurements, with the mean calculated for analysis.

7. **Sustained Cold Response** was tested using a newly developed wearable peltier thermode (Dhama, India). This battery powered device creates a cool temperature through standard thermo-electric methods but has been designed to be worn on the forearm. The device comprises a 2x3cm thermode plate that is embedded in a rigid arm wrap. The wrap is kept damp in order to facilitate dissipation of the heat produced by the cooling process. The thermode can be set to several different specific temperatures using touch controls and maintains this temperature for up to 5 minutes (Figure 4.1).



Figure 4.1

Photograph of the Dhama thermode system showing the control unit and the pad for application to the arm.

For this study, the Dhama thermode was set to 12°C. Before application to each participant, the external surface was sprayed with water and the thermode plate temperature checked using a thermistor. It was then applied to the participant's ECRB test site for 5 minutes,

using the timer on the Algotect Descriptor Index (ADI) Apple iPad application (see below). On completion of the 5-minute test it was removed from the patient's forearm before being turned off. Response to the sustained cold stimulus was measured using the ADI scales, delivered via an Apple iPad application (Moss, 2013). The ADI combines measures of perceived sensation intensity with a measure of sensory quality. Intensity of sensation was assessed using the 4 calibrated 100mm VAS sliding scales shown on the iPad touch screen (Figure 4.2).

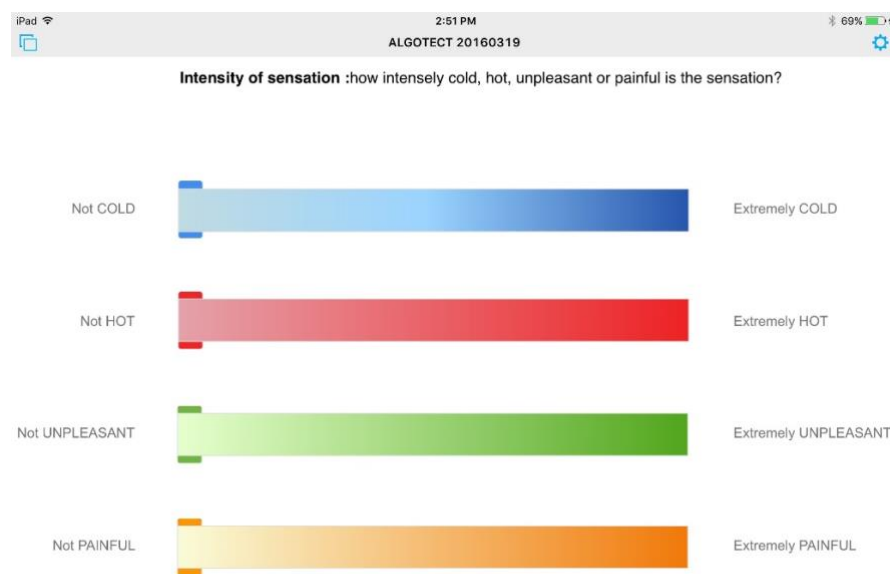


Figure 4.2

Screenshot of the 4 calibrated 100mm VAS sliding scales to assess cold, heat, unpleasantness and pain.

Participants were also asked to select words that best describe the quality of the sensation experienced from a set of descriptors based on the key sensory elements of the McGill Pain Questionnaire descriptor list (Melzack, 1975) (Figure 4.3).

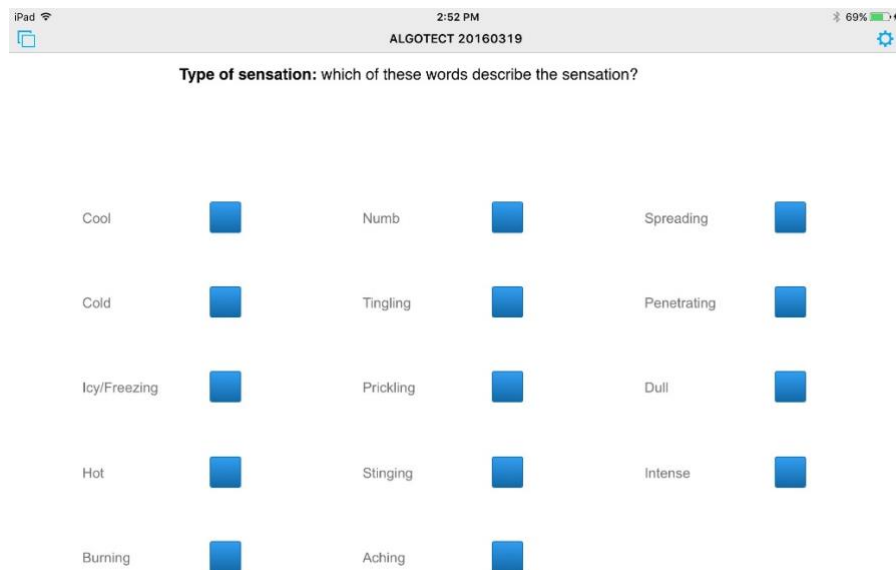


Figure 4.3

Screenshot of the ADI descriptors showing the range of sensory descriptors that can be selected.

Ratings for either intensity or quality were taken every 30-seconds for 5-minutes. A previously developed algorithm was used to calculate a total ADI score based on the combined intensity and quality responses (Moss, 2013). As well as calculating a total sustained cold ADI score (min 0, max 9), a subscore for combined VAS intensity for cold, heat, unpleasantness and pain (max score 4) and a subscore for sensation quality (mean word score (MWS), max score 5) were also calculated, using the method described by Moss (2013).

4.4.4. Power Analysis

Primary hypotheses: An a priori power and sample size analysis was calculated based on anticipated difference between 'good' and 'poor' outcome groups at 6 months post-surgery in self-report, physical and QST measures (primary hypothesis 2). The sample size was calculated using data from Study 1 in patients at 12-18 months post-TKR.

The mean and SD data for good and poor outcome groups for the key QST measures of knee PPT, knee CPT and key self-report measures of PainDETECT and WOMAC Pain are shown in Table 4.2.

Table 4.2: Mean and SD values for Knee PPT, PainDETECT and WOMAC

Total						
	Knee PPT (kPa)		PainDETECT		WOMAC Pain	
	Mean	SD	Mean	SD	Mean	SD
Good						
outcome	416.72	254.83	3.03	3.62	2.13	2.46
group						
Poor						
outcome	282.64	167.92	7.27	5.80	5.77	3.96
group						

Using this data and with alpha set at 0.05, for a power of 80%, it was calculated that a sample size of 108 (108 for knee PPT, 60 for PainDETECT and 96 for WOMAC Pain) would be needed to show a significant difference between groups. The targeted sample size was therefore set at 120 to account for a 10% dropout rate.

Secondary Hypotheses: For the logistic regression required for secondary hypotheses 1, 2 & 3, an initial sample size analysis was completed (alpha set at 0.05; beta at 80%). The widely-accepted assumption of 10 outcomes per predictor variable is assumed. In the previous study (Study 1) the ratio of participants with good to poor KSS outcome at 12 months post-TKR at JRAC was approximately 3:1. It is anticipated that 4 predictor variables will be applied to each of the logistic regression models. This would therefore mean that a sample size of approximately 120 would be needed (30 participants with poor KSS outcomes) (Stoltzfus, 2011).

4.4.5. Data Analysis

Cut off point for mild, moderate and severe pain

For neck pain, the Numeric Rating Scale (NRS) cut off points for mild, moderate and severe pain are 1-3, 4-6 and 7-10 (Fejer et al., 2005). Zelman et al. (2005) established that the NRS cut off points for mild, moderate and severe pain for diabetic peripheral neuropathy are 1-3 (mild), 4-6 (moderate) and 7-10 (severe). For cancer pain, the optimal NRS pain cut off points based on the degree of interference with cancer patients' function for mild, moderate and severe pain are: 1-4 (mild), 5-6 (moderate) and 7-10 (severe) (Serlin et al., 1995). The NRS cut off points for phantom limb pain (mild pain: 1-4, moderate pain: 5-7, severe pain: 8-10), back pain (mild pain: 1-4, moderate pain: 5-6, severe pain: 7-10) and pain 'in general' (mild pain: 1-3, moderate pain: 4-6, severe pain: 7-10) all differ slightly (Jensen et al., 2001).

Due to the slight differences in pain cut off points in the literature, NRS scores of 1-3, 4-6 and 7-10 will be classified as mild, moderate and severe pain for the purposes of this study.

'Good' and 'Poor' Outcome

Outcome at 6 months post-surgery according to the self-report Knee Society Score (KSS) (Insall et al., 1989) of 'good' or 'poor' was used to group patients dichotomously. Group allocation was determined by the pain component of the KSS as per Wright et al. (2014). The pain component of the KSS is categorized as no pain (none), mild or occasional pain (stairs only, walking and stairs), moderate pain (occasional, continual), and severe pain (Insall et al., 1989). Participants who reported no pain and mild or occasional pain were allocated to the 'good' outcome group, and those with moderate to severe pain were allocated to the 'poor' outcome group.

Criterion Variable

At 3 months post-TKR, the criterion variable for the logistic regression model was the average pain (moderate pain and above) felt over the last 4 weeks in the PainDETECT questionnaire (Freyenhagen & Baron, 2006).

At 6 months post-TKR, the criterion variable for the logistic regression model was the KSS outcome (Insall et al., 1989). The KSS has been demonstrated to have adequate convergent construct validity, and its pain and function scores have moderate to strong correlations to the pain and function domains of the WOMAC and SF-36 (Lingard et al., 2001). Participants were classified using the KSS as belonging to either the 'good' or 'poor' outcome group.

Predictor Variables

Predictor variables were selected according to previous studies suggesting likely risk factors for persistent post-operative pain (Elson & Brenkel, 2006; Kehlet et al., 2006; Lunn et al., 2013; Macrae & Davies, 1999; Suokas et al., 2012; Vilardo & Shah, 2011; Wylde et al., 2011; Wylde, Jeffery, et al., 2012). Self-reported measures of pain, function, psychological distress and quality of life and physical / sensory measures were used.

Confounding Variables

A range of confounding variables were also measured. They included age, gender, body mass index (height, weight), smoker or non-smoker and duration of pain pre-operatively. Presence of post-operative infection (prosthesis, respiratory or other) was also recorded as a potentially confounding factor.

Other types of data that were collected from medical notes include analgesia used (pre-operatively, intra-operatively and post-operatively), type of prosthesis used for the knee replacement and surgical approach (Appendix 3). Data with regards to treatment received before (Appendix 4) and after the total knee replacement were also collected (Appendix 5).

IBM SPSS Statistics version 22 was used for the statistical analysis, with alpha set at 0.05. Normality of the data was determined by using the Shapiro-Wilk test, any variable that had $p > 0.05$ was normally distributed. Levene's test was used to confirm whether the data for each group demonstrated equal variance. Degrees of freedom were corrected when equal variances were not assumed ($p < 0.05$).

Group differences were analysed using Independent-Samples t test if the variable was normally distributed, and Mann-Whitney U test was used if the variable was not normally distributed.

Logistic regression was used to determine the predictive value of a range of key measures (quantitative sensory testing, PainDETECT score, functional level, quality of life and psychological distress) in determining persistent pain post-TKR. Variables that were significant in the test for group differences were entered into the univariate logistic regression. Following that, multivariate logistic regression analysis was performed by entering the variables that showed significance on the univariate logistic regression analysis.

In addition, receiver operating characteristic (ROC) curve analysis was used to determine the sensitivity and specificity of any measures identified in the logistic regression model in terms of their capacity to identify those who did or did not have persistent pain post-surgery. All data were reported as mean \pm standard deviation. Significant results were considered as $p < 0.05$. Table 4.3 shows the statistical tests for each hypotheses.

Table 4.3: Hypotheses and Statistical Test Used

Hypotheses and Related Data	Statistical Analysis
1. Difference in pre-operative baseline measures between 'no to low pain' versus 'moderate to severe pain' groups at 3 months following TKR surgery.	Independent-Samples T tests (Normal data) Mann-Whitney U Tests (Non-normal data)
2. Difference in pre-operative baseline and at 3 months post-surgery measures between participants categorized as showing 'poor' versus 'good' outcome groups at 6 months following TKR surgery	Independent-Samples T tests (Normal data) Mann-Whitney U Tests (Non-normal data)
3. Predicting membership of the moderate to severe pain group at 3 months post-surgery using pre-operative baseline measures.	Logistic Regression ROC Curve Analysis

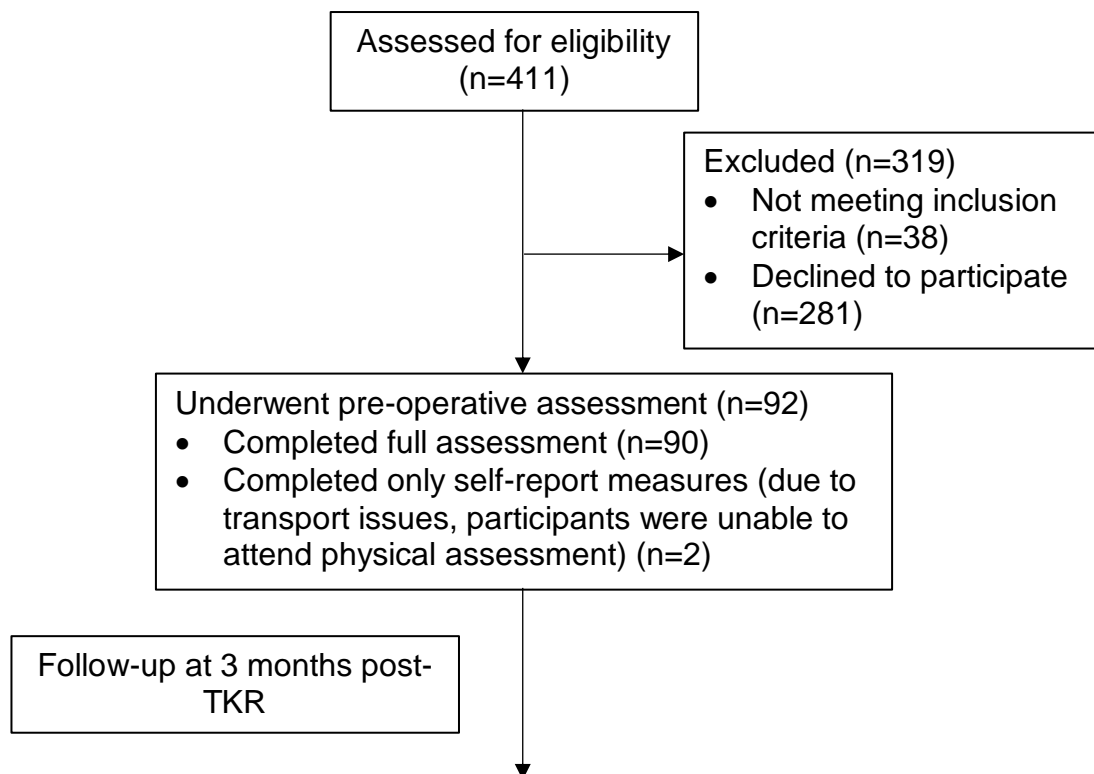
- | | |
|--|---|
| 4. Predicting membership of the 'poor' outcome group at 6 months post-surgery using pre-operative baseline measures. | Logistic Regression
ROC Curve Analysis |
| 5. Predicting membership of the 'poor' outcome group at 6 months post-surgery using pre-operative baseline CPT. | ROC Curve Analysis |
| 6. Predicting membership of the 'poor' outcome group at 6 months post-surgery using pre-operative baseline PainDETECT. | ROC Curve Analysis |
-

4.5. Results

4.5.1. Recruitment of participants

A total of ninety-two participants took part in the study.

Figure 4.4 shows the participant numbers and loss to follow-up through the phases of the study.



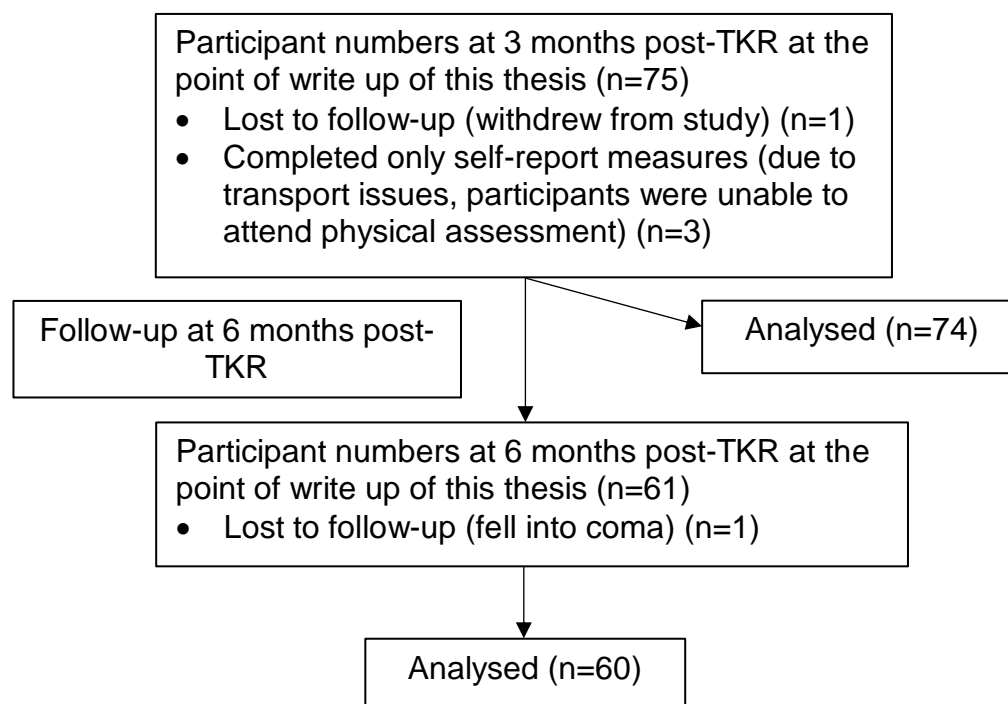


Figure 4.4

Flow diagram of participants through the phases of the study.

4.5.2. Pain level at 3 months post-TKR

Participant demographics at 3 months post-TKR

At 3 months post-surgery, there were seventy-four participants whose data were used for analysis. Fifty-seven participants in the ‘no to low pain’ (Numeric Rating Scale (NRS) < 4 group (twenty-three male and thirty-four female: mean age 70.03 ± 7.26 , range 51-82) and seventeen participants in the ‘moderate to severe pain’ (NRS ≥ 4) group (seven male and ten female: mean age 67.65 ± 7.68 , range 55-80) (Table 4.4).

Table 4.4: Participant demographics at 3 months post-TKR

	No to Low Pain group (n = 57)	Moderate to Severe Pain group (n = 17)
Gender (M : F)	23 : 34	7 : 10
Age (years)	70.03 ± 7.26	67.65 ± 7.68
Age (range)	51 to 82	55 to 80

Primary Hypothesis 1:

There will be a difference at pre-operative baseline in measures of QST, pain, functional level, health status, psychological distress and sleep quality between participants categorized as having 'no to mild pain' (<4 in NRS pain) versus 'moderate to severe pain' (≥4 in NRS pain) at 3 months following TKR surgery.

- **Quantitative Sensory Testing**

Pressure Pain Threshold

There were no significant differences between the 'no to mild pain' and 'moderate to severe pain' groups for pre-operative pressure pain threshold across all test sites (Table 4.5).

Table 4.5: Pre-operative PPT (kPa) (3 months post-TKR)

Site	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Ipsilateral ECRB	282.88	121.71	289.02	140.58	0.893
Contralateral Knee	349.87	180.92	267.56	133.99	0.079
Ipsilateral Knee	337.06	203.03	327.54	171.99	0.923
All sites (Average)	323.27	157.86	294.71	135.28	0.594

* Indicates statistical significance at $p \leq 0.05$

Heat Detection and Heat Pain Thresholds

Pre-operatively, the 'moderate to severe pain' group detected changes in heat sensation significantly later than the 'no to mild pain' group at the contralateral knee ($p=0.001$), but not at the ECRB site ($p=0.115$) and the operated knee ($p=0.537$). Pre-operative heat pain thresholds were not significantly different across all sites between groups.

Taking an average of readings at all sites, there was a significant difference in pre-operative heat detection threshold ($p=0.023$) between the 'no to mild pain' and 'moderate to severe pain' groups (Table 4.6).

Table 4.6: Pre-operative HDT and HPT (°C) (3 months post-TKR)

Site	Test	No to Mild Pain		Moderate to Severe Pain		p
		Mean	SD	Mean	SD	
Ipsilateral	HDT	36.23	2.79	37.16	3.1	0.115
ECRB	HPT	46.19	3.18	47.15	3.26	0.154
Contralateral	HDT	37.19	3.53	40.24	4.06	0.001*
Knee	HPT	44.9	3.46	45.66	4.32	0.247
Ipsilateral	HDT	37.44	3.6	38.16	4.12	0.537
Knee	HPT	44.59	3.8	46.27	3.27	0.095
All Sites	HDT	36.95	2.63	38.53	2.92	0.023*
Average	HPT	45.23	2.9	46.35	2.78	0.112

* Indicates statistical significance at $p \leq 0.05$

Cold Detection and Cold Pain Thresholds

The 'moderate to severe pain' group demonstrated a reduction in sensory acuity as compared to the 'no to mild pain' group, perceiving cold at a significantly lower temperature at the ECRB site ($p=0.049$). Cold pain thresholds were not significantly different across all sites between groups. Taking an average of readings at all sites, there were no significant group differences in pre-operative cold detection ($p=0.073$) and cold pain threshold ($p=0.974$) (Table 4.7).

Table 4.7: Pre-operative CDT and CPT (°C) (3 months post-TKR)

Site	Test	No to Mild Pain		Moderate to Severe Pain		p
		Mean	SD	Mean	SD	
Ipsilateral	CDT	28.25	2.68	26.23	3.87	0.049*
ECRB	CPT	5.64	7.48	7.87	10.21	0.680
Contralateral	CDT	27.54	2.94	26.71	2.54	0.125
Knee	CPT	6.84	9.71	6.21	10.16	0.766
Ipsilateral	CDT	28.1	1.96	26.69	3.14	0.082
Knee	CPT	8.77	9.75	10.26	11.15	0.573

All Sites	CDT	27.96	2.23	26.55	2.82	0.073
Average	CPT	7.09	7.63	8.11	9.53	0.974

* Indicates statistical significance at $p \leq 0.05$

Vibration Detection Threshold

The 'moderate to severe pain' group detected changes in vibration sensation significantly later than the 'no to mild pain' group across all 3 test sites (ECRB: $p < 0.001$; Contralateral knee: $p < 0.001$; Operated knee: $p < 0.001$). This demonstrated that the 'moderate to severe pain' group had reduced sensory acuity as compared to the 'no to mild pain' group (Table 4.8).

Table 4.8: Pre-operative VDT (μm) (3 months post-TKR)

Site	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Ipsilateral ECRB	4.06	2.85	13.51	10.81	$<0.001^*$
Contralateral Knee	6.61	7.39	18.88	16.05	$<0.001^*$
Ipsilateral Knee	7.64	9.92	20.81	16.97	$<0.001^*$
All Sites (Average)	6.1	5.95	17.73	13.33	$<0.001^*$

* Indicates statistical significance at $p \leq 0.05$

Sustained Cold Response

There were no significant differences in the pre-operative sustained cold response ADI scores between groups (Table 4.9).

Table 4.9: Pre-operative Sustained Cold Response ADI (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	

ADI VAS	1.26	1.09	1.76	1.39	0.189
MWS	2.45	0.76	2.46	0.68	0.867
ADI Total	3.71	1.51	4.23	1.76	0.226

* Indicates statistical significance at $p \leq 0.05$

- **Pain**

PainDETECT

The 'moderate to severe pain' group had significantly higher scores in pre-operative Pain (Now) ($p=0.003$) and Pain (Average) ($p=0.037$) as compared to the 'no to mild pain' group (Table 4.10).

Table 4.10: Pre-operative Pain levels (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Pain (Now)	2.82	2.3	4.88	2.47	0.003*
Pain (Strongest)	6.58	2.24	7.53	1.94	0.102
Pain (Average)	4.63	2.03	5.82	2.01	0.037*

* Indicates statistical significance at $p \leq 0.05$

The pre-operative PainDETECT scores were significantly higher in the 'moderate to severe pain' group ($p<0.001$). The mean value for the 'moderate to severe pain' group was 13.88 suggesting that a neuropathic pain component could be present in some members of this group (Table 4.11).

Table 4.11: Pre-operative PainDETECT score (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
PainDETECT	7.70	4.47	13.88	6.49	<0.001*

* Indicates statistical significance at $p \leq 0.05$

PQAS

The 'moderate to severe pain' group scored significantly higher for the pre-operative PQAS Paroxysmal ($p=0.008$) and PQAS Deep ($p=0.001$) quality factors (Table 4.12).

Table 4.12: Pre-operative PQAS Quality Factors (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Paroxysmal	12.65	8.84	20.18	10.48	0.008*
Superficial	2.88	4.44	7.53	12.5	0.217
Deep	13.38	8.74	22.65	11.26	0.001*

* Indicates statistical significance at $p \leq 0.05$

PCS

The 'moderate to severe pain' group scored higher on all 3 subscales of the PCS, but there were only significant differences in the Rumination ($p=0.038$) and Magnification ($p=0.001$) subscales. The 'moderate to severe pain' group also scored significantly higher on the total score of the PCS ($p=0.016$) (Table 4.13).

Table 4.13: Pre-operative PCS scores (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Rumination	3.02	3.37	5.41	4.56	0.038*
Magnification	1.39	1.92	2.82	1.81	0.001*
Helplessness	3.37	3.88	4.94	4.01	0.071
Total	7.77	8.41	13.18	9.31	0.016*

* Indicates statistical significance at $p \leq 0.05$

- **Functional Level**

ALF

The 'moderate to severe pain' group were significantly slower pre-operatively in the ALF Walk ($p=0.018$) and Transfer ($p=0.002$) components as compared to the 'no to mild pain' group (Table 4.14). The ALF Stairs component was not analysed as the data set was incomplete due to the lack of a suitable stairs assessment area for 35 participants.

Table 4.14: Pre-operative ALF (Secs) (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
8 Metre Walk	8.89	3.84	10.26	3.62	0.018*
Transfer	10.39	4.16	15.54	10.76	0.002*
Total	19.27	7.76	25.8	14.2	0.003*

* Indicates statistical significance at $p \leq 0.05$

ROM

There were no significant group differences in both pre-operative active and passive range of motion at the operated knee (Table 4.15).

Table 4.15: Pre-operative ROM of operated knee (Degrees) (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Flexion (AROM)	113.03	15.46	110.81	17.08	0.571
Extension (AROM)**	4.39	4.38	5.55	5.4	0.445
Flexion (PROM)	116.78	16.26	113.84	18.71	0.700

Extension (PROM)**	3.58	4.17	4.81	5.16	0.339
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* Indicates statistical significance at $p \leq 0.05$

** Extension values are expressed as lack of degrees to full extension

Knee Extensor Strength

There was no significant difference in pre-operative knee extensor strength across groups ($p=0.264$) (Table 4.16).

Table 4.16: Pre-operative knee extensor strength (Kg) (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Knee Extensor Strength	18.28	8.83	15.02	5.8	0.264

* Indicates statistical significance at $p \leq 0.05$

• Health status

SF-36

There were significant differences in the SF-36 PF ($p=0.024$), BP ($p=0.002$), GH ($p=0.009$), VT ($p=0.017$), SF ($p=0.037$), MH($p=0.05$) and PCS (0.004) health domains between the 'no to mild pain' and 'moderate to severe pain' groups (Table 4.17). These results indicate that the 'moderate to severe pain' group had more limitations in performing physical activities (PF), higher levels of pain that impacted on normal activities (BP), a belief that they were in worse health (GH), lower energy levels (VT), ability to perform normal social activities was hampered due to interference from physical or emotional problems (SF), increased feelings of nervousness and depression (MH) and more limitations in physical functioning and role participation due to physical problems, a high degree of bodily pain, and poor general health (PCS).

Table 4.17: Pre-operative SF-36 scores (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
PF	40.54	24.55	25	16.96	0.024*
RP	52.08	28.18	37.5	27.51	0.072
BP	48.75	17.57	32.94	18.82	0.002*
GH	78.28	16.71	64.65	20.23	0.009*
VT	57.13	24.28	42.28	20.79	0.017*
SF	78.01	25.19	61.76	28.46	0.037*
RE	75.73	27.47	68.63	32.48	0.464
MH	81.84	14.66	71.18	20.96	0.05*
PCS	38.60	7.77	32.24	7.65	0.004*
MCS	55.52	10.1	50.86	13.52	0.21

* Indicates statistical significance at $p \leq 0.05$

SCQ

There was no significant group difference in the number of co-morbid conditions reported ($p=0.07$). However, it is interesting to note that the 'moderate to severe pain' group was afflicted on average with 3 more co-morbidities as compared to the 'no to mild pain' group (Table 4.18).

Table 4.18: Pre-operative SCQ (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
SCQ	6.42	3.1	9.41	6.06	0.07

* Indicates statistical significance at $p \leq 0.05$

WOMAC

The 'moderate to severe pain' group scored significantly higher on the pre-operative WOMAC Pain ($p < 0.001$), WOMAC Function ($p = 0.001$) and WOMAC Total ($p < 0.001$) scores, indicating that they had higher levels of pain and more difficulty with daily activities as compared to the 'no to mild pain' group (Table 4.19).

Table 4.19: Pre-operative WOMAC scores (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Pain	7.89	3.2	11.82	4.25	<0.001*
Stiffness	3.81	1.38	4.65	1.5	0.075
Function	26.91	11.25	37.88	11.96	0.001*
Total	38.61	14.86	54.35	17.03	<0.001*

* Indicates statistical significance at $p \leq 0.05$

• Psychological distress

PHQ-8

The 'moderate to severe pain' group scored significantly higher on the pre-operative PHQ-8 as compared to the 'no to mild pain' group ($p = 0.002$) (Table 4.20). Based on the PHQ-8 scoring system, the 'moderate to severe pain' group was classified on average as having mild depression. The respective surgeons were informed if their participants ($n = 10$) had a score of ≥ 10 on the PHQ-8.

Table 4.20: Pre-operative PHQ-8 score (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
PHQ-8	3.58	3.99	7.88	6.24	0.002*

* Indicates statistical significance at $p \leq 0.05$

Sleep Quality

The 'moderate to severe pain' group scored significantly lower in PSQI sleep quality ($p=0.004$) and day dysfunction ($p=0.036$), indicating that they had worse sleep quality and an increase in daytime disruption as compared to the 'no to mild pain' group (Table 4.21).

Table 4.21: Pre-operative PSQI scores (3 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Sleep quality	1.04	0.76	1.76	0.83	0.004*
Sleep latency	1.32	1.09	1.47	1.33	0.714
Sleep duration	1.12	0.98	1.47	1.07	0.216
Sleep efficiency	1.12	1.25	1.47	1.23	0.271
Sleep disturbances	1.53	1.39	1.71	0.66	0.079
Sleep medications	0.54	1	0.82	1.29	0.463
Day dysfunction	0.81	0.72	1.18	0.39	0.036*
Total	7.47	4.38	9.88	5.02	0.079

* Indicates statistical significance at $p \leq 0.05$

Secondary Hypothesis 1:

Pre-operative baseline measures (which may include cold pain threshold (CPT), pressure pain threshold (PPT), PainDETECT score, WOMAC score, psychological distress or sleep quality index score) will predict pain levels at 3 months post-TKR surgery.

Univariate Logistic Regression

A range of pre-operative variables were statistically significant in the univariate logistic regression analysis. These included body mass index, a range of QST measures, ALF measures, a range of pain report measures, the PHQ8 score, sleep quality measures and several components of the SF-36. The univariate logistic regression results are in table 4.22.

Table 4.22: Logistic regression (univariate) for 'moderate to severe pain' group at 3 months post-surgery

Univariate Logistic Regression			
	OR	95%CI (OR)	p
BMI	1.11	(1.01, 1.23)	0.027*
Ipsilateral ECRB CDT	1.03	(0.97, 1.10)	0.325
Contralateral Knee HDT	1.21	(1.05, 1.39)	0.007*
HDT All Sites Average	1.22	(1.01, 1.47)	0.045*
Ipsilateral ECRB VDT	1.46	(1.21, 1.77)	<0.001*
Contralateral Knee VDT	1.10	(1.04, 1.17)	0.002*
Ipsilateral Knee VDT	1.08	(1.03, 1.13)	0.002*
VDT All Sites Average	1.15	(1.06, 1.25)	0.001*
ALF 8 Metre Walk	1.09	(0.96, 1.24)	0.206
ALF Transfer	1.14	(1.02, 1.28)	0.024*
ALF Total	1.14	(1.02, 1.28)	0.018*
WOMAC Pain	1.36	(1.13, 1.63)	0.001*
WOMAC Function	1.09	(1.03, 1.15)	0.003*
WOMAC Total	1.07	(1.02, 1.11)	0.002*
Pre-operative Pain Now	1.42	(1.11, 1.81)	0.005*
Pre-operative Pain Average	1.34	(1.01, 1.78)	0.042*
PainDETECT	1.24	(1.10, 1.41)	0.001*
PCS Rumination	1.17	(1.02, 1.34)	0.030*
PCS Magnification	1.40	(1.07, 1.84)	0.015*
PQAS Paroxysmal Quality Factor	1.09	(1.02, 1.15)	0.008*
PQAS Deep Quality Factor	1.10	(1.03, 1.17)	0.003*
PHQ8	1.19	(1.05, 1.35)	0.006*
PSQI Sleep Quality	3.20	(1.48, 6.91)	0.003*
PSQI Day Dysfunction	2.35	(0.99, 5.56)	0.052
SF36 PF	0.97	(0.94, 1.00)	0.022*
SF36 BP	0.95	(0.92, 0.99)	0.005*
SF36 GH	0.96	(0.93, 0.99)	0.011*
SF36 VT	0.98	(0.95, 1.00)	0.031*
SF36 SF	0.98	(0.96, 1.00)	0.032*

SF36 PCS	0.89	(0.81, 0.97)	0.008*
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* Indicates statistical significance at $p \leq 0.05$

Multivariate Logistic Regression

Multivariate logistic regression analysis was performed by entering the pre-operative variables that showed significance on the univariate logistic regression analysis. 3 logistic regression models were considered (Physical measures only, Self-report measures only and Combined measures).

Physical measures

The physical measures multivariate logistic regression analysis identified ipsilateral ECRB VDT as the sole pre-operative physical measures predictor of membership into the 'moderate to severe pain' group at 3 months post-TKR surgery (Table 4.23).

Table 4.23: Logistic regression (multivariate) for 'moderate to severe pain' group at 3 months post-surgery (Physical measures)

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
Ipsilateral ECRB VDT	1.46	(1.21, 1.77)	<0.001*

* Indicates statistical significance at $p \leq 0.05$

ROC curve analysis was performed on ipsilateral ECRB VDT to ascertain the cut-off point, as well as its sensitivity and specificity (Figure 4.5).

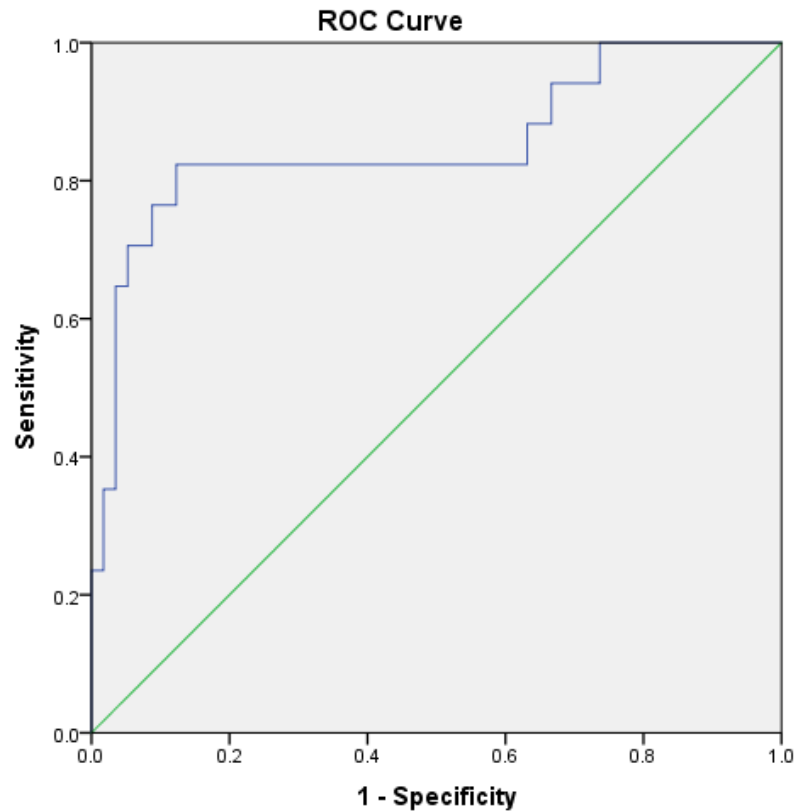


Figure 4.5

ROC curve for pre-operative ipsilateral ECRB VDT.

The area under the curve (AUC) was 0.852 (95% CI: 0.73, 0.98) ($p < 0.001$), indicating that pre-operative ipsilateral ECRB VDT testing was significantly better than chance in predicting membership into the 'moderate to severe pain' group at 3 months post-TKR surgery (Table 4.24).

Table 4.24: AUC for pre-operative ipsilateral ECRB VDT

Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
			Lower Bound	Upper Bound
0.852	0.063	0.000*	0.73	0.98

* Indicates statistical significance at $p \leq 0.05$

A pre-operative ipsilateral ECRB VDT reading of 6.97 μ m (sensitivity: 0.824, specificity 0.877) gave a positive likelihood ratio of 1.46 for membership into the 'moderate to severe pain' group at 3 months post-TKR surgery.

Self-report measures

The self-report measures multivariate logistic regression analysis identified PainDETECT and the PHQ8 questionnaire as pre-operative self-report measures that predict membership into the 'moderate to severe pain' group at 3 months post-TKR surgery (Table 4.25).

Table 4.25: Logistic regression (multivariate) for 'moderate to severe pain' group at 3 months post-surgery (Self-report measures)

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
PainDETECT	1.22	(1.07, 1.39)	0.003*
PHQ8	1.15	(1, 1.33)	0.045*

* Indicates statistical significance at $p \leq 0.05$

ROC curve analysis was performed on PainDETECT and PHQ8 scores to ascertain the cut-off point, as well as the sensitivity and specificity of these measures (Figure 4.6).

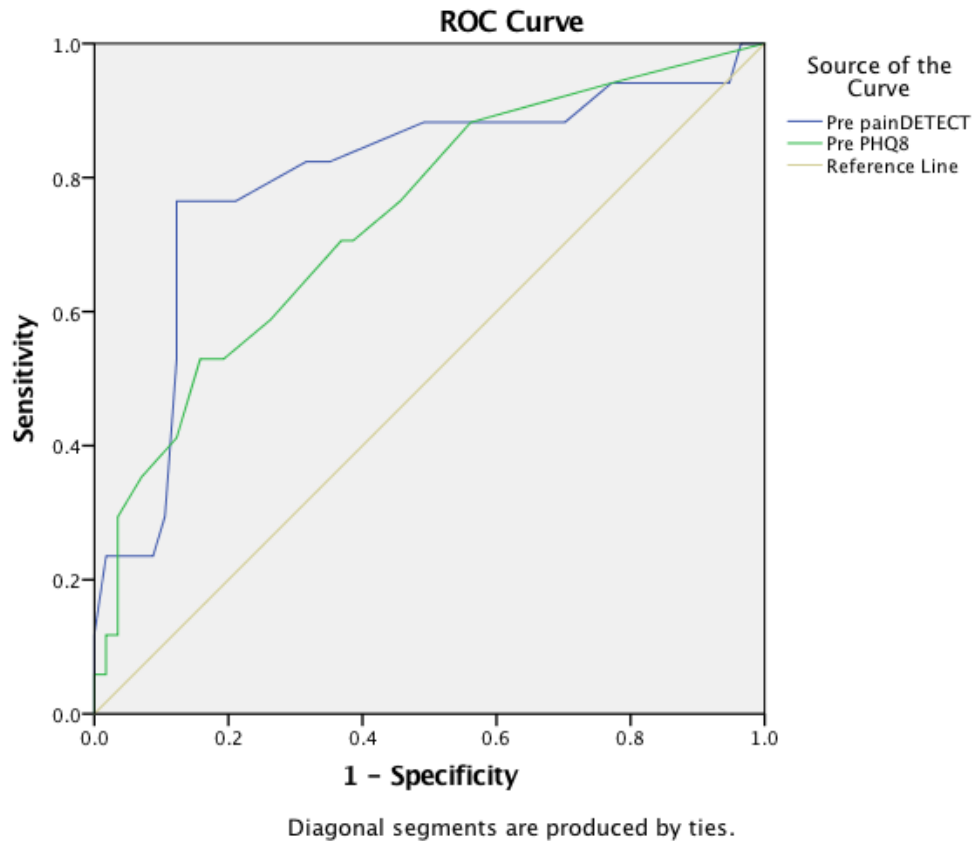


Figure 4.6

ROC curves for pre-operative PainDETECT and PHQ8.

The AUC for pre-operative PainDETECT was 0.798 (95% CI: 0.66, 0.93) ($p < 0.001$) and pre-operative PHQ8 was 0.741 (95% CI: 0.60, 0.88) indicating that these 2 self-report measures were significantly better than chance in predicting membership into the 'moderate to severe pain' group at 3 months post-TKR surgery (Table 4.26).

Table 4.26: AUC for pre-operative PainDETECT and PHQ8

Test	Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
				Lower Bound	Upper Bound
PainDETECT	0.798	0.069	<0.001*	0.66	0.93
PHQ8	0.741	0.07	0.003*	0.60	0.88

* Indicates statistical significance at $p \leq 0.05$

A pre-operative PainDETECT score of 11.5 (sensitivity: 0.765, specificity 0.877) gave a positive likelihood ratio of 1.22, and a pre-operative PHQ8 score of 4.5 (sensitivity: 0.706, specificity 0.632) gave a positive likelihood ratio of 1.15 for membership into the ‘moderate to severe pain’ group at 3 months post-TKR surgery.

Combined measures

The significant variables (pre-operative ipsilateral ECRB VDT, PainDETECT and PHQ8) that were identified from the above 2 models (Physical and Self-report measures) were entered into a combined multivariate logistic regression analysis.

Pre-operative ipsilateral ECRB VDT and PainDETECT were then identified as predictors for membership into the ‘moderate to severe pain’ group at 3 months post-TKR surgery. (Table 4.27).

Table 4.27: Logistic regression (multivariate) for ‘moderate to severe pain’ group at 3 months post-surgery (Combined measures)

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
Ipsilateral ECRB VDT	1.38	(1.13, 1.68)	0.002*
PainDETECT	1.16	(1.01, 1.34)	0.041*

* Indicates statistical significance at $p \leq 0.05$

ROC curve analysis was performed on pre-operative ipsilateral ECRB VDT and PainDETECT measures to determine the cut-off point of the individual measures and their respective sensitivity and specificity (Figure 4.7).

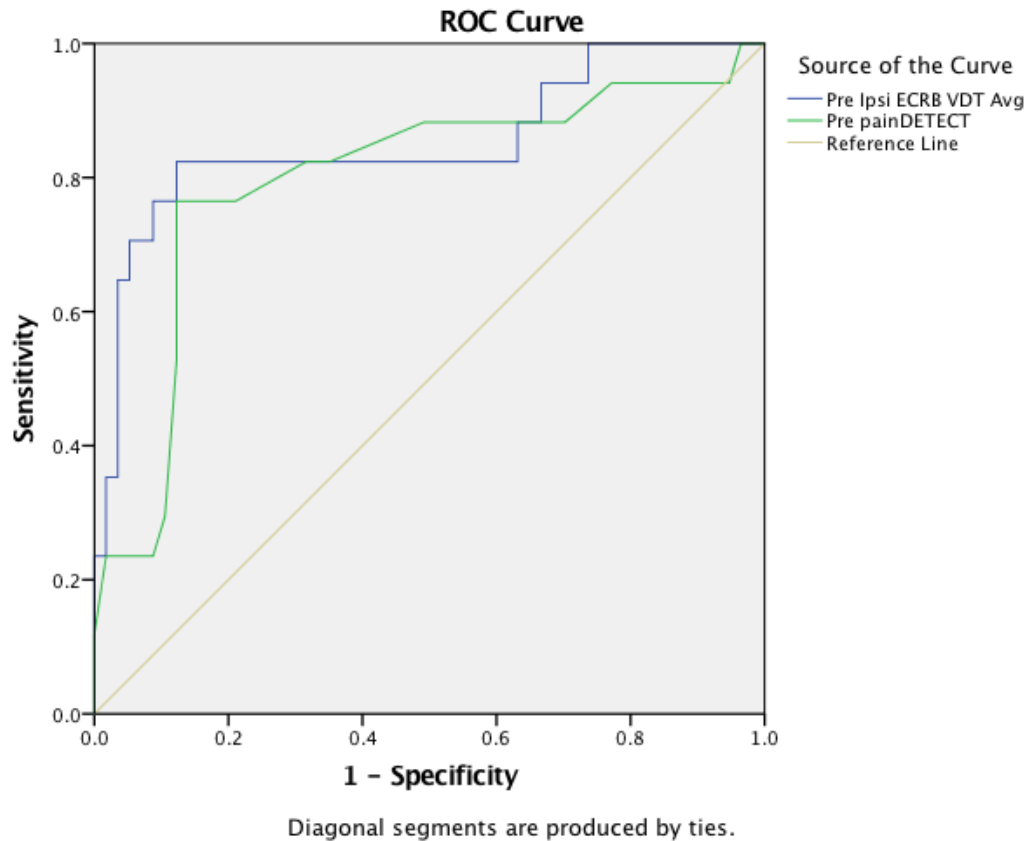


Figure 4.7

ROC curves for pre-operative ipsilateral ECRB VDT and PainDETECT.

The AUC for pre-operative ipsilateral ECRB VDT was 0.852 (95% CI: 0.73, 0.98) ($p < 0.001$) and PainDETECT was 0.787 (95% CI: 0.66, 0.93) ($p = 0.007$) indicating that these measures were significantly better than chance in predicting membership into the 'moderate to severe pain' group at 3 months post-TKR surgery (Table 4.28).

Table 4.28: AUC for pre-operative ipsilateral ECRB VDT and PainDETECT

Measure	Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
				Lower Bound	Upper Bound
Ipsilateral ECRB VDT	0.852	0.063	<0.001*	0.73	0.98
PainDETECT	0.798	0.069	0.000*	0.66	0.93

* Indicates statistical significance at $p \leq 0.05$

A pre-operative ipsilateral ECRB VDT reading of 6.97 μ m (sensitivity: 0.824, specificity 0.877) gave a positive likelihood ratio of 1.38 and a PainDETECT score of 11.5 (sensitivity: 0.765, specificity: 0.877) gave a positive likelihood ratio of 1.16 for membership into the 'moderate to severe pain' group at 3 months post-TKR surgery.

Model Fit

Model fit for the combined measures (pre-operative ipsilateral ECRB VDT and pre-operative PainDETECT) multivariate logistic regression was analysed using the 'Omnibus Tests of Model Coefficients' and the 'Hosmer and Lemeshow Test'.

Based on the results of the 'Omnibus Tests of Model Coefficients', the model for the combined measures (pre-operative ipsilateral ECRB VDT and pre-operative PainDETECT) multivariate logistic regression is statistically significant ($p < 0.0005$) (Table 4.29).

The results of the model summary indicate that there is a 38% probability of being in the 'moderate to severe pain' group at 3 months (Table 4.30)

The results of the 'Hosmer and Lemeshow Test' is not statistically significant ($p = 0.199$), indicating that the model is not a poor fit (Table 4.31).

Table 4.29: Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	30.505	1	0.000
	Block	30.505	1	0.000
	Model	30.505	1	0.000
Step 2	Step	4.578	1	0.032
	Block	35.083	2	0.000
	Model	35.083	2	0.000

Table 4.30: Model Summary

	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
Step 1	49.260	0.338	0.512
Step 2	44.681	0.378	0.572

Table 4.31: Hosmer and Lemeshow Test

	Chi-Square	df	Sig.
Step 1	13.160	8	0.106
Step 2	11.054	8	0.199

4.5.3. Outcome group at 6 months post-TKR

Participant Demographics at 6 months post-TKR

At 6 months post-surgery, there were sixty participants. Fifty-one participants in the good outcome group (twenty-one male and thirty female: mean age 69.9 ± 7.47 , range 51-82) and nine participants in the poor outcome group (three male and six female: mean age 66.56 ± 7.42 , range 55-77) (Table 4.32).

Table 4.32: Participant demographics at 6 months post-TKR

	Good outcome group (n = 51)	Poor outcome group (n = 9)
Gender (M : F)	21 : 30	3 : 6
Age (years)	69.9 ± 7.47	66.56 ± 7.42
Age (range)	51 to 82	55 to 77

Primary Hypothesis 2:

There will be a difference at pre-operative baseline and at 3 months post-surgery in measures of QST, pain, functional level, health status, psychological distress and sleep quality between participants categorized as showing 'poor' versus 'good' outcomes at 6 months following TKR surgery.

Pre-operative baseline measures

- **Quantitative Sensory Testing**

Pressure Pain Threshold

There were no significant pre-operative differences between groups in PPT at all test sites (Table 4.33).

Table 4.33: Pre-operative PPT (kPa) (6 months post-TKR)

Site	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
Ipsilateral ECRB	289.16	123.05	260.81	121.74	0.425
Contralateral Knee	350.18	177.5	257.83	155.38	0.111
Ipsilateral Knee	341.85	176.98	275.58	156.72	0.305
All sites (Average)	327.06	147.69	264.74	139.4	0.182

* Indicates statistical significance at $p \leq 0.05$

Heat Detection and Heat Pain Thresholds

The poor outcome group detected changes in heat sensation at significantly higher temperatures than the good outcome group at the contralateral knee ($p=0.043$). Pre-operative heat pain thresholds were not significantly different across all sites between groups (Table 4.34).

Table 4.34: Pre-operative HDT and HPT (°C) (6 months post-TKR)

Site	Test	Good Outcome		Poor Outcome		p
		Mean	SD	Mean	SD	
Ipsilateral	HDT	36.5	3.04	37.23	3.25	0.259
ECRB	HPT	46.42	3.03	47.5	2.67	0.329
Contralateral	HDT	37.82	4	40.47	4.21	0.043*
Knee	HPT	45.36	3.3	45.92	4.99	0.362
Ipsilateral	HDT	37.72	3.75	39.01	4.42	0.21
Knee	HPT	45.22	3.38	46.59	3.35	0.255
All Sites	HDT	37.34	2.85	38.91	2.78	0.084
Average	HPT	45.67	2.67	46.67	2.2	0.293

* Indicates statistical significance at $p \leq 0.05$

Cold Detection and Cold Pain Thresholds

There were no significant differences between groups for cold detection and cold pain thresholds across all sites (Table 4.35).

Table 4.35: Pre-operative CDT and CPT (°C) (6 months post-TKR)

Site	Test	Good Outcome		Poor Outcome		p
		Mean	SD	Mean	SD	
Ipsilateral	CDT	27.87	2.85	26.14	3.72	0.159
ECRB	CPT	5.34	7.13	9.51	11.54	0.584
Contralateral	CDT	27.03	2.95	26.39	2.92	0.501
Knee	CPT	7	9.49	6.99	11.35	0.896
Ipsilateral	CDT	27.61	2.25	26.84	3	0.475
Knee	CPT	9.35	9.47	7.98	12.02	0.671
All Sites	CDT	27.5	2.33	26.47	2.9	0.305
Average	CPT	7.23	7.4	8.14	10.88	0.925

* Indicates statistical significance at $p \leq 0.05$

Vibration Detection Threshold

The poor outcome group detected changes in vibration sensation at significantly larger amplitudes than the good outcome group across all 3 test sites (ECRB: $p < 0.001$; Contralateral knee: $p = 0.001$; Operated knee: $p = 0.001$), indicating that the poor outcome group had reduced tactile sensory acuity as compared to the good outcome group (Table 4.36).

Table 4.36: Pre-operative VDT (μm) (6 months post-TKR)

Site	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
Ipsilateral	5.74	7.4	11.54	4.81	<0.001*
ECRB					
Contralateral	7.37	8.99	17.52	12.45	0.001*
Knee					

Ipsilateral Knee	8.18	10.94	20.16	13.67	0.001*
All Sites (Average)	7.10	8.49	16.41	8.02	0.000*

* Indicates statistical significance at $p \leq 0.05$

Sustained Cold Response

There were no significant differences in the pre-operative sustained cold response ADI scores between groups (Table 4.37).

Table 4.37: Pre-operative Sustained Cold Response ADI (6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
ADI VAS	1.31	1.09	2	1.12	0.085
MWS	2.4	0.72	2.43	0.62	0.715
ADI Total	3.71	1.52	4.43	1.28	0.099

* Indicates statistical significance at $p \leq 0.05$

• Pain

PainDETECT

The poor outcome group scored significantly higher in pre-operative Pain (Now) ($p=0.014$) as compared to the good outcome group (Table 4.38).

Table 4.38: Pre-operative Pain levels (6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Pain (Now)	2.94	2.32	5.11	2.26	0.014*
Pain (Strongest)	6.71	2.31	7.33	2	0.474
Pain (Average)	4.69	1.94	6.11	1.76	0.056

* Indicates statistical significance at $p \leq 0.05$

The pre-operative PainDETECT scores were significantly higher for the poor outcome group ($p=0.031$), indicating the possible presence of a neuropathic pain component for some members of this group (Table 4.39).

Table 4.39: Pre-operative PainDETECT score (6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
PainDETECT	8.57	5.22	12.44	4.77	0.031*

* Indicates statistical significance at $p \leq 0.05$

PQAS

The poor outcome group scored significantly higher for the pre-operative PQAS Deep ($p=0.006$) quality factor (Table 4.40).

Table 4.40: Pre-operative PQAS scores (6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Paroxysmal	13.20	9.19	19.11	8.49	0.077
Superficial	3.25	4.38	3.44	5.83	0.605
Deep	14.12	8.83	23.33	8.49	0.006*

* Indicates statistical significance at $p \leq 0.05$

PCS

The poor outcome group scored significantly higher on the PCS Magnification subscale ($p=0.002$) and PCS Total scores ($p=0.032$) (Table 4.41).

Table 4.41: Pre-operative PCS scores (6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Rumination	3.04	3.49	5.67	4.24	0.074

Magnification	1.45	1.99	3.44	1.81	0.002*
Helplessness	3.35	3.9	4.56	2.46	0.082
Total	7.84	8.61	13.67	7.68	0.032*

* Indicates statistical significance at $p \leq 0.05$

- **Functional Level**

ALF

The poor outcome group were significantly slower pre-operatively in the ALF Transfer ($p=0.008$) and ALF Total ($p=0.018$) measures as compared to the good outcome group (Table 4.42). The ALF Stairs component was not analysed as the data set was incomplete due to the lack of a suitable stairs assessment area for 19 participants.

Table 4.42: Pre-operative ALF (Secs) (6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
8 Metre Walk	9.02	3.78	10.94	3.42	0.064
Transfer	10.79	4.22	14.57	4.9	0.008*
Total	19.81	7.73	25.51	7.76	0.018*

* Indicates statistical significance at $p \leq 0.05$

ROM

There were no significant pre-operative differences across groups in both active and passive range of motion of the operated knee (Table 4.43).

Table 4.43: Pre-operative ROM of operated knee (Degrees) (6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Flexion (AROM)	111.63	15.77	107.41	22.62	0.844

Extension (AROM)**	5.02	4.39	5.37	4.59	0.739
Flexion (PROM)	115.05	16.58	111.03	24.47	0.967
Extension (PROM)**	4.18	4.26	4.19	3.81	0.9

* Indicates statistical significance at $p \leq 0.05$

** Extension values are expressed as lack of degrees to full extension

Knee Extensor Strength

There was no significant difference in pre-operative knee extensor strength between groups ($p=0.264$) (Table 4.44).

Table 4.44: Pre-operative knee extensor strength (Kg) (6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
Knee Extensor Strength	16.81	7.85	11.83	5.16	0.072

* Indicates statistical significance at $p \leq 0.05$

• Health status

SF-36

There were significant group differences in the SF-36 PF ($p=0.024$), BP ($p=0.018$), GH ($p=0.002$), VT ($p=0.008$), SF ($p=0.027$), MH($p=0.032$) health domains and PCS (0.008) component summary measure (Table 4.45).

These results indicate that the poor outcome group had more limitations in performing physical activities (PF), higher levels of pain that impacted on normal activities (BP), a belief that they were in poorer health (GH), lower energy levels (VT), ability to perform normal social activities was hampered due to interference from physical or emotional problems (SF), increased feelings of nervousness and depression (MH) and more limitations in

physical functioning and role participation due to physical problems, a high degree of bodily pain, and poor general health (PCS).

Table 4.45: Pre-operative SF-36 scores (6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
PF	37.86	23.31	18.89	14.95	0.018*
RP	49.39	28.84	29.86	19.21	0.057
BP	48.33	17.62	27.89	14.99	0.002*
GH	77.39	17.01	61	15.75	0.008*
VT	55.76	25.09	36.81	19.63	0.027*
SF	78.12	24.27	55.56	30.69	0.034*
RE	75.98	28.22	62.04	28.9	0.16
MH	81.18	15.28	67.22	18.89	0.032*
PCS	37.7	7.59	30.13	7.97	0.008*
MCS	55.63	10.73	48.48	11.94	0.084

* Indicates statistical significance at $p \leq 0.05$

SCQ

The poor outcome group had significantly more co-morbid conditions as compared to the good outcome group ($p=0.005$) (Table 4.46).

Table 4.46: Pre-operative SCQ (6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
SCQ	6.41	3.24	11.44	5.81	0.005*

* Indicates statistical significance at $p \leq 0.05$

WOMAC

The poor outcome group scored significantly higher on the pre-operative WOMAC Pain ($p<0.001$), WOMAC Function ($p=0.007$) and WOMAC Total ($p=0.003$) scores, indicating that they had higher levels of pain and more

difficulty with daily activities as compared to the good outcome group (Table 4.47).

Table 4.47: Pre-operative WOMAC scores (6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Pain	8.06	3.32	12.67	3.71	<0.001*
Stiffness	3.96	1.34	4.56	1.42	0.293
Function	28.43	11.12	39.44	10.19	0.007*
Total	40.45	14.76	56.67	14.4	0.003*

* Indicates statistical significance at $p \leq 0.05$

- **Psychological distress**

PHQ-8

The poor outcome group scored significantly higher on the pre-operative PHQ-8 as compared to the good outcome group ($p=0.001$) (Table 4.48).

Based on the PHQ-8 scoring system, the poor outcome group is classified as having mild depression on average. The respective surgeons were informed if their patients ($n=10$) had a score of ≥ 10 on the PHQ-8.

Table 4.48: Pre-operative PHQ-8 score (6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
PHQ-8	3.63	4.21	9.11	4.08	0.001*

* Indicates statistical significance at $p \leq 0.05$

Sleep Quality

There were no significant group differences in the pre-operative PSQI scores (Table 4.49).

Table 4.49: Pre-operative PSQI scores (6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Sleep quality	1.06	0.7	1.56	1.01	0.163
Sleep latency	1.33	1.16	1.33	1.22	0.991
Sleep duration	1.12	0.97	1.33	1	0.516
Sleep efficiency	1.08	1.21	1.44	1.13	0.309
Sleep disturbances	1.57	1.46	1.67	0.5	0.167
Sleep medications	0.49	1.01	1.11	1.45	0.153
Day dysfunction	0.86	0.72	1.11	0.33	0.267
Total	7.51	4.38	9.56	4.39	0.163

* Indicates statistical significance at $p \leq 0.05$

3 months post-surgery measures

• Quantitative Sensory Testing

Pressure Pain Threshold

There were no significant differences at 3 months post-surgery between groups in PPT values across all test sites (Table 4.50).

Table 4.50: 3 months post-TKR PPT (kPa) (outcome at 6 months post-TKR)

Site	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
Ipsilateral ECRB	322.64	125.98	242.93	99	0.088
Contralateral Knee	357.24	142.99	284.33	84.48	0.145
Ipsilateral Knee	365.07	168.74	292.68	148.17	0.187
All sites (Average)	348.31	138.46	273.31	99.71	0.114

* Indicates statistical significance at $p \leq 0.05$

Heat Detection and Heat Pain Thresholds

There were no significant differences at 3 months post-surgery between groups across all heat detection and heat pain threshold test sites (Table 4.51).

Table 4.51: 3 months post-TKR HDT and HPT (°C) (outcome at 6 months post-TKR)

Site	Test	Good Outcome		Poor Outcome		p
		Mean	SD	Mean	SD	
Ipsilateral	HDT	36	2.5	37.42	3.9	0.35
ECRB	HPT	46.54	3	46.84	3.61	0.667
Contralateral	HDT	37.73	3.8	39.26	3.9	0.163
Knee	HPT	45.66	2.94	46.56	3.21	0.334
Ipsilateral	HDT	38.34	3.92	39.88	4.34	0.096
Knee	HPT	45.92	2.81	46.23	3.33	0.636
All Sites	HDT	37.35	2.98	38.86	3.12	0.109
Average	HPT	46.04	2.53	46.54	2.82	0.547

* Indicates statistical significance at $p \leq 0.05$

Cold Detection and Cold Pain Thresholds

There were no significant differences between groups for cold detection and cold pain thresholds across all sites (Table 4.52).

Table 4.52: 3 months post-TKR CDT and CPT (°C) (outcome at 6 months post-TKR)

Site	Test	Good Outcome		Poor Outcome		p
		Mean	SD	Mean	SD	
Ipsilateral	CDT	27.84	2.9	27.52	4.18	0.889
ECRB	CPT	4.5	5.67	9.99	11.83	0.282
Contralateral	CDT	27.3	2.62	28.28	2.28	0.153
Knee	CPT	5.73	8.52	12.7	11.99	0.101
Ipsilateral	CDT	27.86	2.34	26.77	3.3	0.396
Knee	CPT	7.47	8.5	12.49	11.23	0.182
All Sites	CDT	27.67	2.27	27.5	3.04	0.88
Average	CPT	0.07	0.13	0.03	0.1	0.38

* Indicates statistical significance at $p \leq 0.05$

Vibration Detection Threshold

There were no significant group differences at 3 months post-surgery in vibration detection thresholds across all sites (Table 4.53).

Table 4.53: 3 months post-TKR VDT (μm) (outcome at 6 months post-TKR)

Site	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
Ipsilateral ECRB	3.52	2.43	4.37	1.56	0.08
Contralateral Knee	5.47	7.53	8.03	9.33	0.273
Ipsilateral Knee	5.85	9.19	8.72	9.91	0.088
All Sites (Average)	4.95	5.91	7.04	6.6	0.169

* Indicates statistical significance at $p \leq 0.05$

Sustained Cold Response

There were no significant differences in the 3 months post-surgery sustained cold response ADI scores between groups (Table 4.54).

Table 4.54: 3 months post-TKR Sustained Cold Response ADI (outcome at 6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
ADI VAS	1.08	1.11	1.78	1.2	0.103
MWS	2.3	0.7	2.6	0.63	0.236
ADI Total	3.42	1.64	4.38	1.69	0.124

* Indicates statistical significance at $p \leq 0.05$

- **Pain**

PainDETECT

The poor outcome group had significantly higher scores in Pain (Now) ($p<0.001$), Pain (Strongest) ($p<0.001$) and Pain (Average) ($p<0.001$) as compared to the good outcome group (Table 4.55).

Table 4.55: 3 months post-TKR Pain levels (outcome at 6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Pain (Now)	0.88	1.03	3.11	1.17	$<0.001^*$
Pain (Strongest)	2.53	2.39	6.56	2.13	$<0.001^*$
Pain (Average)	1.43	1.4	4.78	1.39	$<0.001^*$

* Indicates statistical significance at $p \leq 0.05$

The 3 months post-surgery PainDETECT scores were significantly higher in the poor outcome group ($p=0.001$), indicating the possible presence of a neuropathic pain component in some members of this group (Table 4.56).

Table 4.56: 3 months post-TKR PainDETECT score (outcome at 6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
PainDETECT	6.04	5.73	13.22	4.29	0.001^*

* Indicates statistical significance at $p \leq 0.05$

PQAS

The poor outcome group scored significantly higher for the 3 months post-surgery PQAS Paroxysmal ($p=0.001$) and PQAS Deep ($p<0.001$) quality factors (Table 4.57).

Table 4.57: 3 months post-TKR PQAS score (outcome at 6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Paroxysmal	5.2	7.69	16.67	10.48	0.001*
Superficial	4.82	7.06	7	7.75	0.341
Deep	5.73	7.57	17.89	6.9	<0.001*

* Indicates statistical significance at $p \leq 0.05$

PCS

The poor outcome group scored significantly higher on all 3 subscales of the PCS (Rumination ($p=0.013$), Magnification ($p<0.001$) and Helplessness ($p=0.010$)) and PCS Total ($p=0.001$) at 3 months post TKR (Table 4.58).

Table 4.58: 3 months post-TKR PCS scores (outcome at 6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Rumination	0.94	1.89	3.44	3.81	0.013*
Magnification	0.29	0.83	2.11	1.62	<0.001*
Helplessness	1.12	2.1	4.56	6.06	0.01*
Total	2.35	4.4	10.11	9.57	0.001*

* Indicates statistical significance at $p \leq 0.05$

• Functional Level

ALF

There were no significant group differences in the ALF. The ALF Stairs component was not analysed as the data set was incomplete due to the lack of a suitable stairs assessment area for 19 participants (Table 4.59).

Table 4.59: 3 months post-TKR ALF (Secs) (outcome at 6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
8 Metre Walk	7.95	2.45	8.95	2.56	0.16
Transfer	8.76	2.62	11.99	7.27	0.144
Total	16.71	4.86	20.94	9.72	0.147

* Indicates statistical significance at $p \leq 0.05$

ROM

There were no significant group differences in 3 months post-surgery active and passive range of motion of the operated knee (Table 4.60).

Table 4.60: 3 months post-TKR ROM of operated knee (Degrees) (outcome at 6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Flexion (AROM)	110.23	13.65	106.92	16.41	0.755
Extension (AROM)**	1.53	2.05	2.44	3.28	0.618
Flexion (PROM)	114.57	13.4	110.67	16.47	0.554
Extension (PROM)**	1.01	1.35	2	2.69	0.479

* Indicates statistical significance at $p \leq 0.05$

** Extension values are expressed as lack of degrees to full extension

Knee Extensor Strength

There was no significant difference in 3 months post-surgery knee extensor strength between groups (Table 4.61).

Table 4.61: 3 months post-TKR knee extensor strength (Kg) (outcome at 6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
Knee Extensor Strength	21.72	7.62	16.91	6.73	0.083

* Indicates statistical significance at $p \leq 0.05$

- **Health status**

SF-36

There were significant group differences in all of the 3 months post-surgery SF-36 health domains (PF ($p<0.001$), RP ($p=0.01$), BP ($p<0.001$), GH ($p=0.032$), VT ($p=0.002$), SF ($p=0.002$), RE ($p=0.003$), MH($p=0.009$)), as well as both PCS (0.008) and MCS ($p=0.023$) component summary measures (Table 4.62). These results indicate that the poor outcome group had more limitations in performing physical activities (PF), had issues performing work or daily activities due to physical problems (RP), had higher levels of pain that impacted on normal activities (BP), a belief that they were in poorer health (GH), had lower energy levels (VT), frequent interference with normal social activities due to physical or emotional problems (SF), had problems with work or other activities due to emotional problems (RE), frequent feelings of nervousness and depression (MH), had limitations in physical functioning and role participation due to physical problems (PCS) and had frequent psychological distress, social and role disability due to emotional problems and poor general health (MCS).

Table 4.62: 3 months post-TKR SF-36 scores (outcome at 6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
PF	64.61	24.18	31.11	16.91	$<0.001^*$
RP	68.01	27.91	41.67	23.39	0.01^*

BP	66.67	21.5	35.67	9.91	<0.001*
GH	79.39	16.51	66.22	19.95	0.032*
VT	62.75	20.12	38.19	20.36	0.002*
SF	83.58	21.72	55.56	21.75	0.002*
RE	87.58	20.51	66.67	19.54	0.003*
MH	83.63	13.42	70.56	13.1	0.009*
PCS	45.84	9.04	34.48	8.63	0.001*
MCS	55.91	8.5	48.38	8.87	0.023*

* Indicates statistical significance at $p \leq 0.05$

SCQ

The poor outcome group had significantly more co-morbid conditions as compared to the good outcome group ($p=0.025$) (Table 4.63).

Table 4.63: 3 months post-TKR SCQ (outcome at 6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
SCQ	5.33	3.5	9.44	5.96	0.025*

* Indicates statistical significance at $p \leq 0.05$

WOMAC

The poor outcome group scored significantly higher on the 3 months post-surgery WOMAC Pain ($p=0.001$), WOMAC Stiffness ($p=0.024$), WOMAC Function ($p=0.001$) and WOMAC Total ($p=0.001$) scores, indicating that they had higher levels of pain, more stiffness and more difficulty with daily activities as compared to the good outcome group (Table 4.64).

Table 4.64: 3 months post-TKR WOMAC scores (outcome at 6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	

Pain	3.1	3.32	8.33	3.71	0.001*
Stiffness	2.51	1.53	4.11	1.83	0.024*
Function	13.37	11.13	27.33	8.03	0.001*
Total	18.98	15.21	39.78	12.55	0.001*

* Indicates statistical significance at $p \leq 0.05$

- **Psychological distress**

PHQ-8

The poor outcome group scored significantly higher on the 3 months post-surgery PHQ-8 as compared to the good outcome group ($p < 0.001$) (Table 4.65). Based on the PHQ-8 scoring system, the poor outcome group is classified as having mild depression. The respective surgeons were informed if their patients ($n=10$) had a score of ≥ 10 on the PHQ-8.

Table 4.65: 3 months post-TKR PHQ-8 score (outcome at 6 months post-TKR)

	Good Outcome		Poor Outcome		p
	Mean	SD	Mean	SD	
PHQ-8	3.1	3.61	9	3.32	$<0.001^*$

* Indicates statistical significance at $p \leq 0.05$

Sleep Quality

There were significant group differences for 3 months post-surgery PSQI Sleep Quality ($p=0.029$), Sleep Disturbances ($p=0.001$), Sleep Medications ($p=0.049$), Day Dysfunction ($p=0.04$) and Total score ($p=0.022$) (Table 4.66). This indicates that the poor outcome group had poorer sleep quality, more disturbances from sleep, increased consumption of over the counter sleep medications and more daytime dysfunction as compared to the good outcome group.

Table 4.66: 3 months post-TKR PSQI scores (outcome at 6 months post-TKR)

	No to Mild Pain		Moderate to Severe Pain		p
	Mean	SD	Mean	SD	
Sleep quality	1.14	0.78	1.89	0.93	0.029*
Sleep latency	1.27	1.1	1.67	1.22	0.35
Sleep duration	1.06	1.05	1.33	1.22	0.529
Sleep efficiency	1.22	1.24	1.89	1.17	0.109
Sleep disturbances	1.37	1.2	1.89	0.33	0.001*
Sleep medications	0.51	0.99	1.33	1.41	0.049*
Day dysfunction	0.71	0.58	1.11	0.33	0.04*
Total	7.27	4.44	11.11	3.92	0.022*

* Indicates statistical significance at $p \leq 0.05$

Secondary Hypothesis 2:

Pre-operative baseline measures (which may include cold pain threshold (CPT), pressure pain threshold (PPT), PainDETECT score, WOMAC score, psychological distress or sleep quality index score) will predict 'poor' outcome at 6 months post-TKR surgery.

Univariate Logistic Regression

A range of pre-operative variables were statistically significant in the univariate logistic regression analysis. The significant univariate logistic regression results are in table 4.67. These included a range of QST measures, ALF measures, a range of pain report measures, the PHQ8 score and several components of the SF-36.

Table 4.67: Logistic regression (univariate) for 'poor' outcome group at 6 months post-TKR

	Univariate Logistic Regression		
	OR	95%CI (OR)	p
Contralateral Knee HDT	1.15	(0.98, 1.38)	0.084

Ipsilateral ECRB VDT	1.08	(0.99, 1.18)	0.075
Contralateral Knee VDT	1.08	(1.01, 1.14)	0.015*
Ipsilateral Knee VDT	1.07	(1.01, 1.12)	0.014*
VDT All Sites Average	1.09	(1.02, 1.17)	0.015*
ALF Transfer	1.16	(1.01, 1.34)	0.031*
ALF Total (Walk + Transfer)	1.08	(1, 1.16)	0.065
WOMAC Pain	1.48	(1.14, 1.94)	0.004*
WOMAC Function	1.1	(1.02, 1.18)	0.015*
WOMAC Total	1.08	(1.02, 1.14)	0.009*
Pain Now	1.5	(1.06, 2.10)	0.021*
Pain Average	1.48	(0.99, 2.22)	0.054
PainDETECT	1.14	(1, 1.30)	0.052
PCS Magnification	1.47	(1.07, 2.02)	0.016*
PCS Total	1.07	(0.99, 1.16)	0.074
PQAS Deep Quality Factor	1.11	(1.02, 1.21)	0.012*
SCQ	1.31	(1.08, 1.58)	0.006*
PHQ8	1.28	(1.07, 1.51)	0.006*
SF36 PF	0.95	(0.9, 1)	0.031*
SF36 BP	0.92	(0.88, 0.98)	0.007*
SF36 GH	0.95	(0.91, 0.99)	0.017*
SF36 VT	0.97	(0.94, 1)	0.045*
SF36 SF	0.97	(0.94, 1)	0.026*
SF36 MH	0.95	(0.91, 0.99)	0.027*
SF36 PCS	0.86	(0.76, 0.97)	0.017*

* Indicates statistical significance at $p \leq 0.05$

Multivariate Logistic Regression

Multivariate logistic regression analysis was performed on the pre-operative variables that were significant on the univariate logistic regression analyses. 3 logistic regression models were considered (Physical measures only, Self-report measures only and Combined measures).

Physical measures

The physical measures multivariate logistic regression analysis identified VDT all sites average as the sole pre-operative physical measures predictor of membership into the 'poor' outcome group at 6 months post-TKR surgery (Table 4.68).

Table 4.68: Logistic regression (multivariate) for 'poor' outcome group at 6 months post-surgery (Physical measures)

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
VDT All Sites Average	1.09	(1.01, 1.18)	0.029*
ALF Transfer	1.15	(1, 1.37)	0.057

* Indicates statistical significance at $p \leq 0.05$

ROC curve analysis was performed on VDT all sites average to ascertain the cut-off point, as well as its sensitivity and specificity (Figure 4.8).

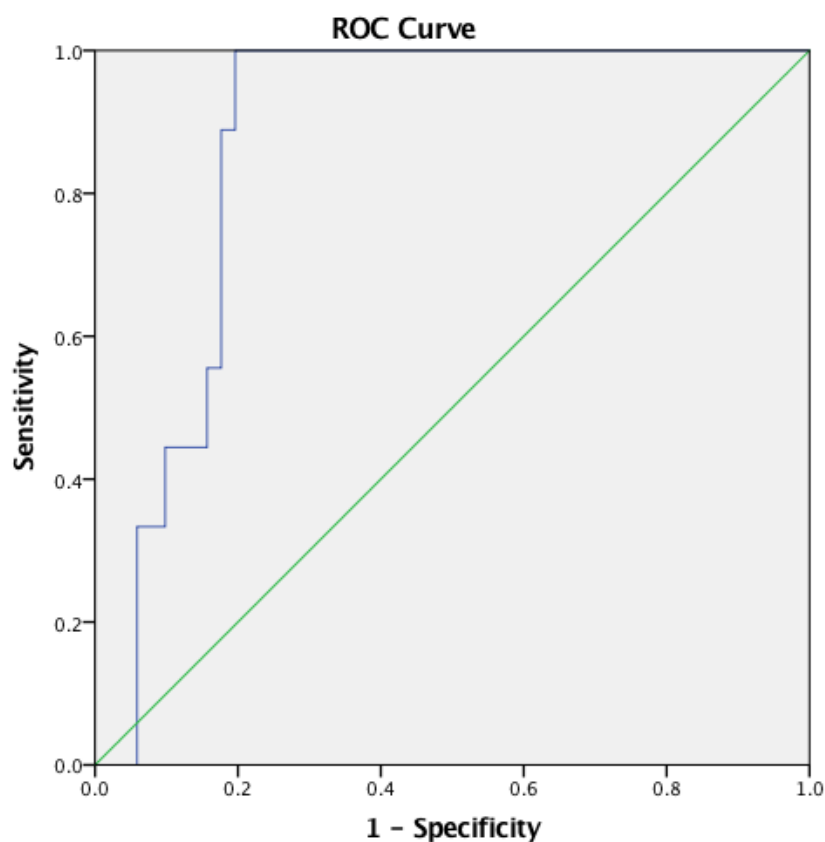


Figure 4.8

ROC curve for pre-operative VDT All Sites Average.

The AUC was 0.871 (95% CI: 0.78, 0.96) (p=0.000), indicating that pre-operative VDT All Sites Average was significantly better than chance in predicting membership into the 'poor' outcome group at 6 months post-TKR surgery (Table 4.69).

Table 4.69: AUC for pre-operative VDT All Sites Average

Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
			Lower Bound	Upper Bound
0.871	0.045	0.000*	0.78	0.96

* Indicates statistical significance at $p \leq 0.05$

A pre-operative VDT All Sites Average reading of 8.04µm (sensitivity: 1, specificity 0.804) gave a positive likelihood ratio of 1.09 of membership into the 'poor' outcome group at 6 months post-TKR surgery.

Self-report measures

The self-report measures multivariate logistic regression analysis identified WOMAC Pain as the pre-operative self-report measure that predicted membership into the 'poor' outcome group at 6 months post-TKR surgery (Table 4.70).

Table 4.70: Logistic regression (multivariate) for 'poor' outcome group at 6 months post-surgery (Self-report measures)

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
WOMAC Pain	1.37	(1.04, 1.8)	0.025*
SCQ	1.23	(0.99, 1.53)	0.063

* Indicates statistical significance at $p \leq 0.05$

ROC curve analysis was performed on WOMAC Pain to determine the cut-off point, as well as its sensitivity and specificity (Figure 4.9).

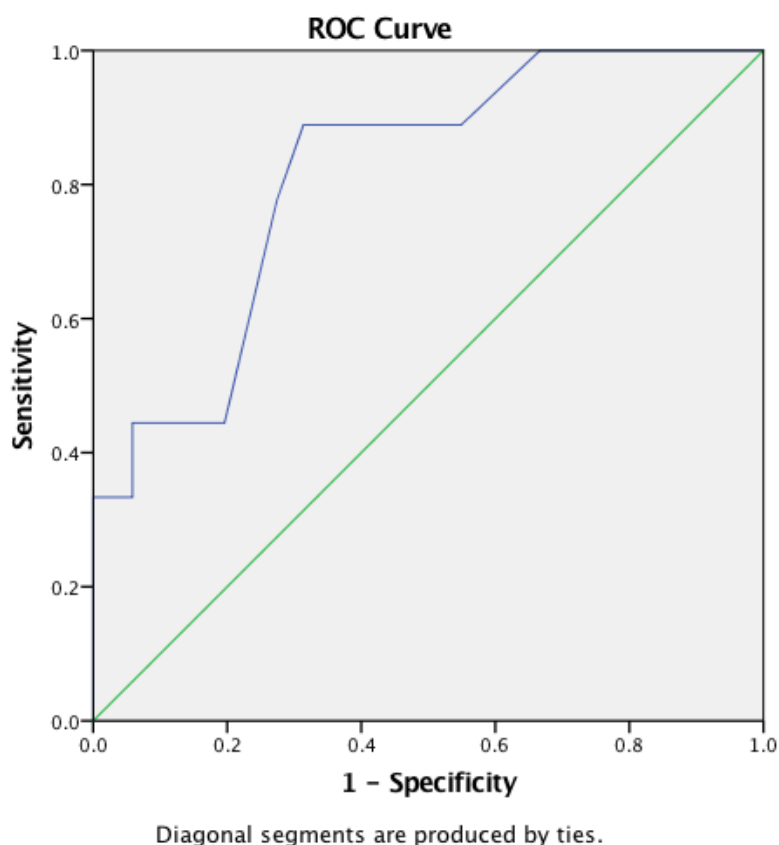


Figure 4.9

ROC curve for pre-operative WOMAC Pain.

The AUC for pre-operative WOMAC Pain was 0.815 (95% CI: 0.68, 0.96) ($p=0.003$) indicating that was significantly better than chance in predicting membership into the 'poor' outcome group at 6 months post-TKR surgery (Table 4.71).

Table 4.71: AUC for pre-operative WOMAC Pain

Test	Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
				Lower Bound	Upper Bound
WOMAC Pain	0.815	0.071	0.003*	0.68	0.96

* Indicates statistical significance at $p \leq 0.05$

A pre-operative WOMAC Pain score of 10.5 (sensitivity: 0.778, specificity 0.725) gave a positive likelihood ratio of 1.37 of membership into the 'poor' outcome group at 6 months post-TKR surgery.

Combined measures

The significant variables (pre-operative VDT All Sites Average and WOMAC Pain) that were identified from the above 2 models (Physical and Self-report measures) were then combined in an all measures multivariate logistic regression model.

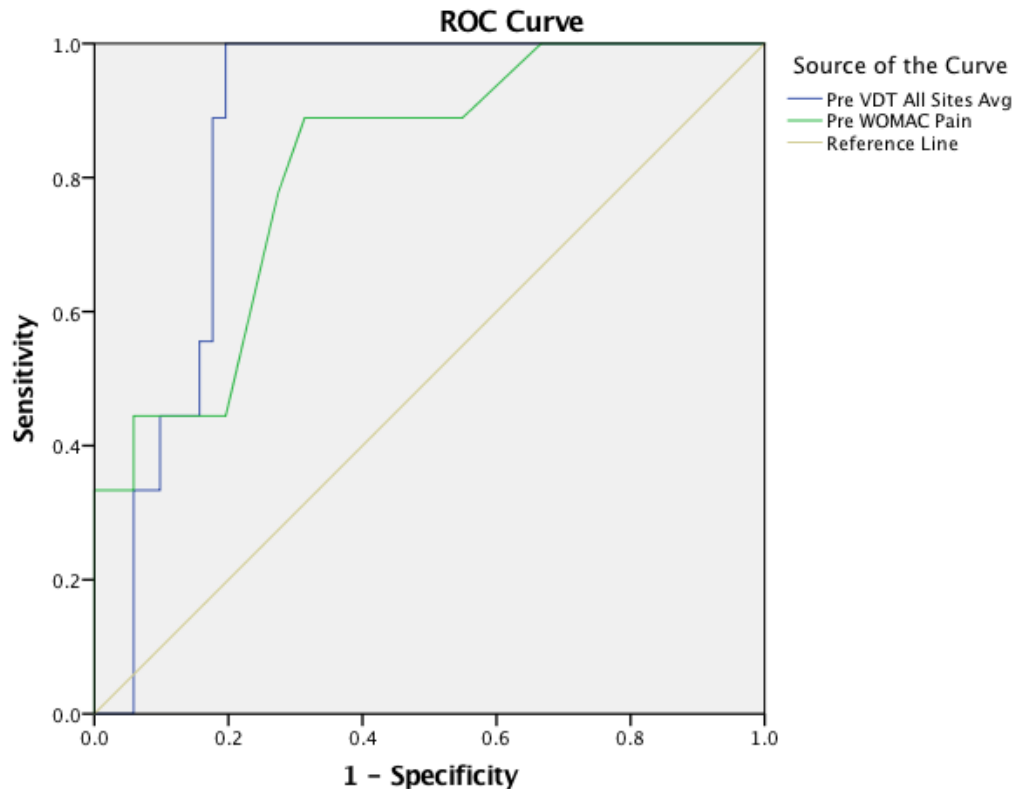
Pre-operative VDT All Sites Average and WOMAC Pain were then identified as predictors for membership into the poor outcome group at 6 months post-TKR surgery (Table 4.72).

Table 4.72: Logistic regression (multivariate) for 'poor' outcome group at 6 months post-surgery (All measures)

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
VDT All Sites Average	1.09	(1.01, 1.18)	0.03*
WOMAC Pain	1.5	(1.11, 2.03)	0.008*

* Indicates statistical significance at $p \leq 0.05$

ROC curve analysis was performed on pre-operative VDT All Sites Average and WOMAC Pain to determine the cut-off point of the individual measures and their respective sensitivity and specificity (Figure 4.10).



Diagonal segments are produced by ties.

Figure 4.10

ROC curves for pre-operative VDT All Sites Average and WOMAC Pain.

The AUC for pre-operative VDT All Sites Average was 0.84 (95% CI: 0.72, 0.96) ($p < 0.001$) and WOMAC Pain was 0.815 (95% CI: 0.68, 0.96) ($p = 0.003$) indicating that these measures were significantly better than chance in predicting membership into the 'poor' outcome group at 6 months post-TKR surgery (Table 4.73).

Table 4.73: AUC for pre-operative VDT All Sites Average and WOMAC Pain

Measure	Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
				Lower Bound	Upper Bound
VDT All Sites Average	0.871	0.045	<0.001*	0.78	0.96

WOMAC Pain	0.815	0.071	0.003*	0.68	0.96
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* Indicates statistical significance at $p \leq 0.05$

A pre-operative VDT All Sites Average of 9.2µm (sensitivity: 0.889, specificity 0.824) gave a positive likelihood ratio of 1.09 and a WOMAC Pain score of 10.5 (sensitivity: 0.778, specificity 0.725) gave a positive likelihood ratio of 1.5 for membership into the 'poor' outcome group at 6 months post-TKR surgery.

Model Fit

Model fit for the combined measures (pre-operative VDT All Sites Average and pre-operative WOMAC Pain) multivariate logistic regression was analysed using the 'Omnibus Tests of Model Coefficients' and the 'Hosmer and Lemeshow Test'.

Based on the results of the 'Omnibus Tests of Model Coefficients', the model for the combined measures (pre-operative VDT All Sites Average and pre-operative WOMAC Pain) multivariate logistic regression is statistically significant ($p < 0.0005$) (Table 4.74).

The results of the model summary indicate that there is a 25% probability of being in the poor outcome group at 6 months (Table 4.75).

The results of the 'Hosmer and Lemeshow Test' is not statistically significant ($p = 0.342$), indicating that the model is not a poor fit (Table 4.76).

Table 4.74: Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	12.401	1	0.000
	Block	12.401	1	0.000
	Model	12.401	1	0.000
Step 2	Step	4.689	2	0.030
	Block	17.090	2	0.000
	Model	17.090	2	0.000

Table 4.75: Model Summary

	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
Step 1	38.324	0.187	0.327
Step 2	33.635	0.248	0.434

Table 4.76: Hosmer and Lemeshow Test

	Chi-Square	df	Sig.
Step 1	9.002	8	0.342
Step 2	2.739	8	0.950

Alternative model for pre-op measures predicting pain levels at 3 months post-TKR

Pre-operative ipsilateral ECRB VDT and PainDETECT were identified as predictors for membership into the ‘moderate to severe pain’ group at 3 months post-TKR surgery. Predictors for membership into the ‘poor’ outcome group at 6 months post-TKR surgery were identified as pre-operative VDT All Sites Average and WOMAC Pain. Even though ipsilateral ECRB VDT and VDT All Sites Average are measures of vibration sensitivity and, PainDETECT and WOMAC Pain are both measures of pain. It was interesting to note that there was a difference in the measures identified as predictors for pain groups at 3 and 6 months post-TKR.

The most likely reason for this is due to the difference in participant numbers at these 2 time points.

In order to offer a better comparison, another analysis (investigating pre-operative measures which will predict pain levels at 3 months post-TKR) was completed where only participants who had reached 6 months post-surgery were included.

The results showed that even though pre-operative VDT All Sites Average was still a significant predictor of membership into the ‘moderate to severe’ pain group at 3 months post-TKR, WOMAC Pain was not (Table 4.77).

However, it is important to note that the WOMAC Pain was very close to significance. It is anticipated that once more participants reach the 6 months

post-surgery time point and the analysis is repeated, WOMAC Pain will show statistical significance.

Table 4.77: Logistic regression (multivariate) for ‘moderate to severe pain’ group at 3 months post-surgery

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
VDT All Sites Average	1.13	(1.04, 1.24)	0.004*
WOMAC Pain	1.23	(0.99, 1.53)	0.064

* Indicates statistical significance at $p \leq 0.05$

Model Fit

Model fit for the combined measures (pre-operative VDT All Sites Average and pre-operative WOMAC Pain) multivariate logistic regression was analysed using the ‘Omnibus Tests of Model Coefficients’ and the ‘Hosmer and Lemeshow Test’.

Based on the results of the ‘Omnibus Tests of Model Coefficients’, the model for the combined measures (pre-operative VDT All Sites Average and pre-operative WOMAC Pain) multivariate logistic regression is statistically significant ($p < 0.0005$) (Table 4.78).

The results of the model summary indicate that there is a 30% probability of being in the ‘moderate to severe pain’ group at 3 months (Table 4.79).

The results of the ‘Hosmer and Lemeshow Test’ is not statistically significant ($p = 0.216$), indicating that the model is not a poor fit (Table 4.80).

Table 4.78: Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	18.370	1	0.000
	Block	18.370	1	0.000
	Model	18.370	1	0.000
Step 2	Step	8.028	2	0.005
	Block	26.398	2	0.000
	Model	26.398	2	0.000

Table 4.79: Model Summary

	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
Step 1	61.394	0.220	0.333
Step 2	53.367	0.300	0.455

Table 4.80: Hosmer and Lemeshow Test

	Chi-Square	df	Sig.
Step 1	8.609	8	0.376
Step 2	10.751	8	0.216

Secondary Hypothesis 3:

3 months post-TKR surgery measures (which may include CPT, PPT, PainDETECT score, surgical approach, immediate post-operative pain intensity or pain catastrophising) will predict ‘poor’ outcome at 6 months post-TKR surgery.

Univariate Logistic Regression

A range of 3 months post-TKR measures were statistically significant in the univariate logistic regression analysis. The univariate logistic regression results are in table 4.81. These included post-operative day 1 pain scores, a range of pain report measures, the PHQ8 score, sleep quality measures and all components of the SF-36.

Table 4.81: Logistic regression (univariate) for ‘moderate to severe pain’ group at 3 months post-surgery

Univariate Logistic Regression			
	OR	95%CI (OR)	p
1st POD NRS Rest	1.73	(1.24, 2.43)	0.001*
1st POD NRS Movt	1.93	(1.36, 2.75)	<0.001*
WOMAC Pain	1.42	(1.14, 1.77)	0.002*
WOMAC Stiffness	1.86	(1.14, 3.05)	0.014*

WOMAC Function	1.11	(1.03, 1.19)	0.004*
WOMAC Total	1.08	(1.03, 1.14)	0.003*
Pain Now (at 3 months)	4.57	(1.82, 11.5)	0.001*
Pain Strongest (at 3 months)	1.78	(1.26, 2.5)	0.001*
Pain Average (at 3 months)	3.78	(1.73, 8.26)	0.001*
PainDETECT	1.22	(1.07, 1.39)	0.004*
PCS Rumination	1.38	(1.05, 1.82)	0.02*
PCS Magnification	2.83	(1.53, 5.24)	0.001*
PCS Helplessness	1.3	(1.03, 1.65)	0.029*
PCS Total	1.2	(1.04, 1.37)	0.011*
PQAS Paroxysmal Quality Factor	1.12	(1.04, 1.21)	0.003*
SCQ	1.23	(1.04, 1.45)	0.016*
PHQ8	1.4	(1.14, 1.72)	0.001*
PSQI Sleep Quality	3.03	(1.2, 7.64)	0.019*
PSQI Sleep Efficiency	1.57	(0.86, 2.86)	0.142
PSQI Sleep Disturbances	1.33	(0.81, 2.17)	0.265
PSQI Sleep Meds	1.79	(1.01, 3.16)	0.047*
PSQI Day Dysfunction	4.18	(0.96, 18.21)	0.057
PSQI Total	1.23	(1.02, 1.47)	0.028*
SF36 PF	0.94	(0.91, 0.98)	0.003*
SF36 RP	0.97	(0.94, 0.99)	0.018*
SF36 BP	0.91	(0.85, 0.97)	0.002*
SF36 GH	0.96	(0.93, 1)	0.051
SF36 VT	0.95	(0.92, 0.99)	0.006*
SF36 SF	0.95	(0.92, 0.99)	0.004*
SF36 RE	0.96	(0.93, 0.99)	0.013*
SF36 MH	0.94	(0.89, 0.99)	0.017*
SF36 PCS	0.87	(0.79, 0.96)	0.006*
SF36 MCS	0.91	(0.84, 0.99)	0.027*

* Indicates statistical significance at $p \leq 0.05$

Multivariate Logistic Regression

Multivariate logistic regression analysis was performed on the 3 months post-TKR variables that showed significance on the univariate logistic regression

analysis. Pain Average (at 3 months) and PCS Total were identified as measures that predict membership into the 'poor' outcome group at 6 months post-TKR surgery (Table 4.82).

Table 4.82: Logistic regression (multivariate) for 'poor' outcome group at 6 months post-surgery

Multivariate Logistic Regression			
	OR	95%CI (OR)	p
Pain Average (at 3 months)	5.42	(1.5, 19.6)	0.01*
PCS Total	1.19	(1.01, 1.39)	0.033*

* Indicates statistical significance at $p \leq 0.05$

ROC curve analysis was performed on 3 months post-TKR data variables PCS Total and Pain Average (at 3 months) to determine the cut-off point of the individual measures and their respective sensitivity and specificity (Figure 4.11).

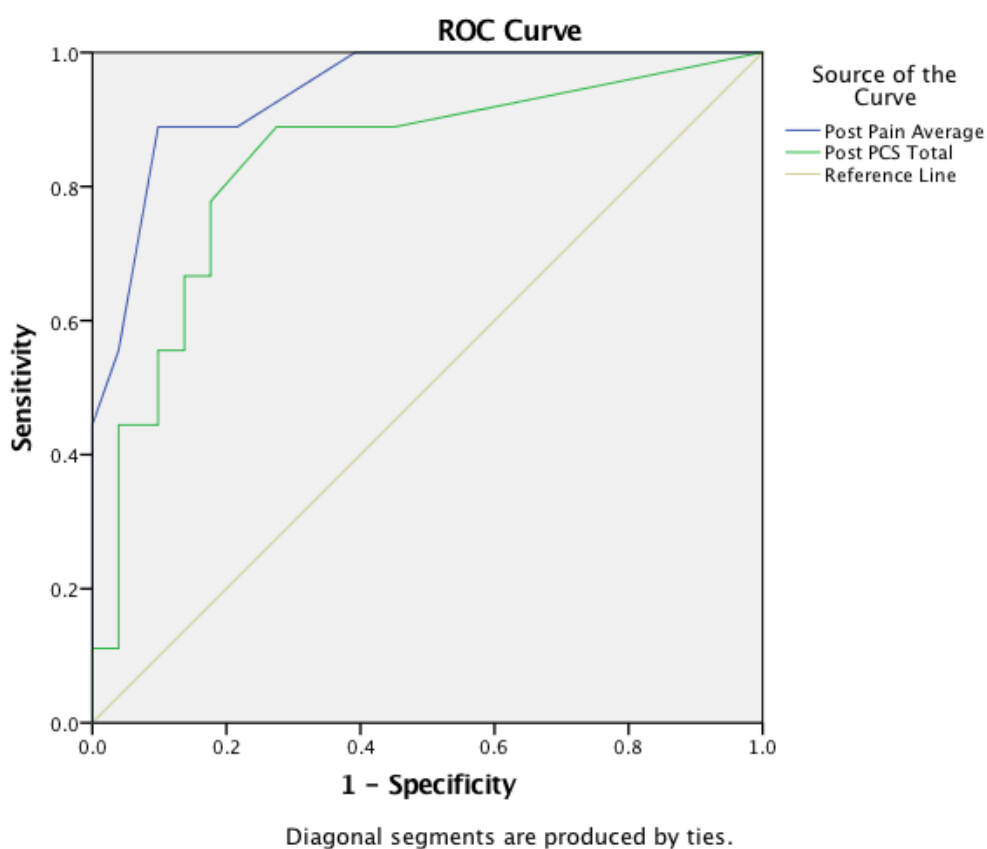


Figure 4.11

ROC curves for 3 months post-TKR PCS Total and Pain Average (at 3 months).

The AUC for PCS Total was 0.836 (95% CI: 0.68, 0.99) ($p=0.001$) and Pain Average (at 3 months) was 0.941 (95% CI: 0.87, 1) ($p=0.000$) indicating that these measures were significantly better than chance in predicting membership into the 'poor' outcome group at 6 months post-TKR surgery (Table 4.83).

Table 4.83: AUC for 3 months post-TKR PCS total and Pain Average (at 3 months)

Measure	Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
				Lower Bound	Upper Bound
PCS Total	0.836	0.078	0.001*	0.68	0.99
Pain Average (at 3 months)	0.941	0.036	0.000*	0.87	1

* Indicates statistical significance at $p \leq 0.05$

A 3 months post-TKR PCS Total score of 3.5 (sensitivity: 0.778, specificity 0.824) gave a positive likelihood ratio of 1.19 and a Pain Average (at 3 months) score of 3.5 (sensitivity: 0.889, specificity 0.902) gave a positive likelihood ratio of 5.42 for membership into the 'poor' outcome group at 6 months post-TKR surgery.

Model Fit

Model fit for the combined measures (3 months post-TKR PCS Total score and 3 months post-TKR Pain Average score) multivariate logistic regression was analysed using the 'Omnibus Tests of Model Coefficients' and the 'Hosmer and Lemeshow Test'.

Based on the results of the 'Omnibus Tests of Model Coefficients', the model for the combined measures (3 months post-TKR PCS Total score and 3 months post-TKR Pain Average score) multivariate logistic regression is statistically significant ($p < 0.0005$) (Table 4.84).

The results of the model summary indicate that there is a 41% probability of being in the 'poor' outcome group at 6 months (Table 4.85).

The results of the 'Hosmer and Lemeshow Test' is not statistically significant ($p = 0.937$), indicating that the model is not a poor fit (Table 4.86).

Table 4.84: Omnibus Tests of Model Coefficients

		Chi-square	df	Sig.
Step 1	Step	26.347	1	0.000
	Block	26.347	1	0.000
	Model	26.347	1	0.000
Step 2	Step	5.684	1	0.017
	Block	32.031	2	0.000
	Model	32.031	2	0.000

Table 4.85: Model Summary

	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
Step 1	24.378	0.355	0.623
Step 2	18.694	0.414	0.725

Table 4.86: Hosmer and Lemeshow Test

	Chi-Square	df	Sig.
Step 1	3.039	4	0.551
Step 2	2.360	4	0.937

Secondary Hypothesis 4:

Baseline CPT values will predict membership into the 'poor' outcome group at 6 months with good sensitivity and specificity.

ROC curve analysis of all pre-operative CPT values determined that they were not able to predict membership into 'poor' outcome group at 6 months post-TKR (Figure 4.12 and Table 4.87).

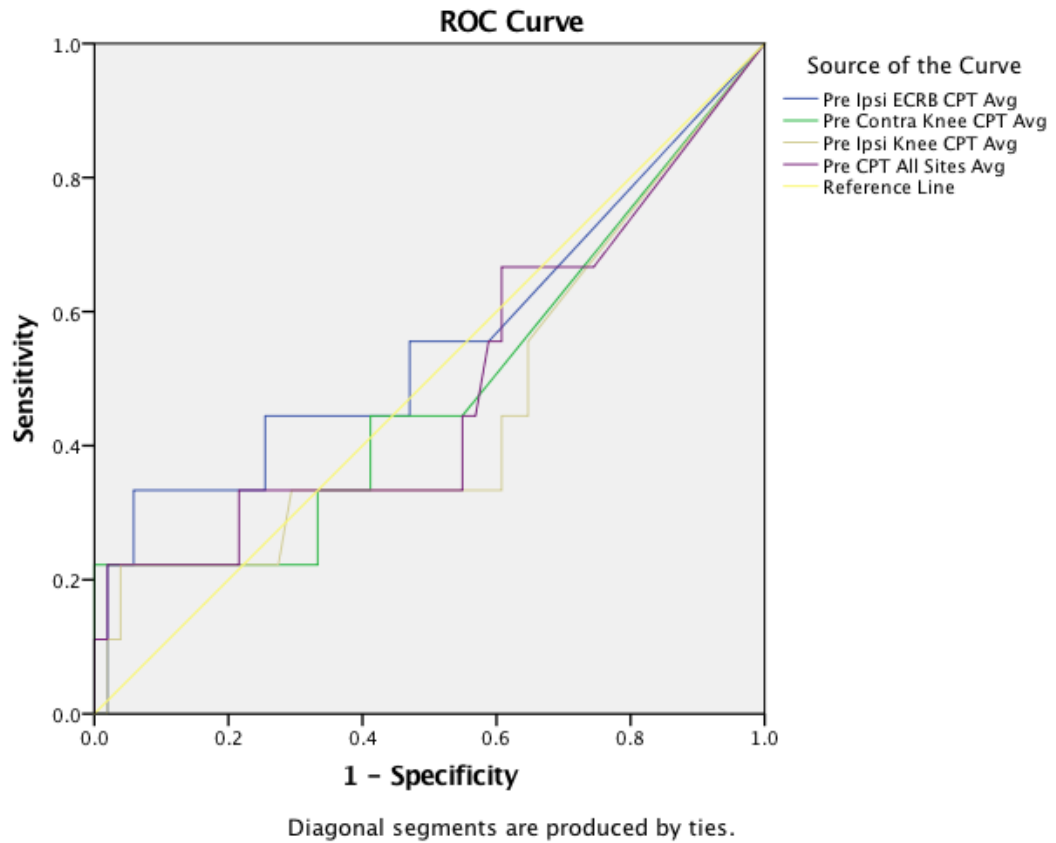


Figure 4.12

ROC curves for pre-operative CPT across all test sites.

Table 4.87: AUC for pre-operative CPT across all test sites

Measure	Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
				Lower Bound	Upper Bound
Ipsilateral ECRB CPT	0.556	0.121	0.598	0.32	0.79
Contralateral Knee CPT	0.487	0.117	0.901	0.26	0.72
Ipsilateral Knee CPT	0.456	0.116	0.679	0.23	0.68
CPT All Sites Average	0.49	0.118	0.926	0.26	0.72

Secondary Hypothesis 5:

Baseline PainDETECT score will predict membership into the ‘poor’ outcome group at 6 months with good sensitivity and specificity.

ROC curve analysis was performed on pre-operative PainDETECT to determine the cut-off point and its sensitivity and specificity (Figure 4.13).

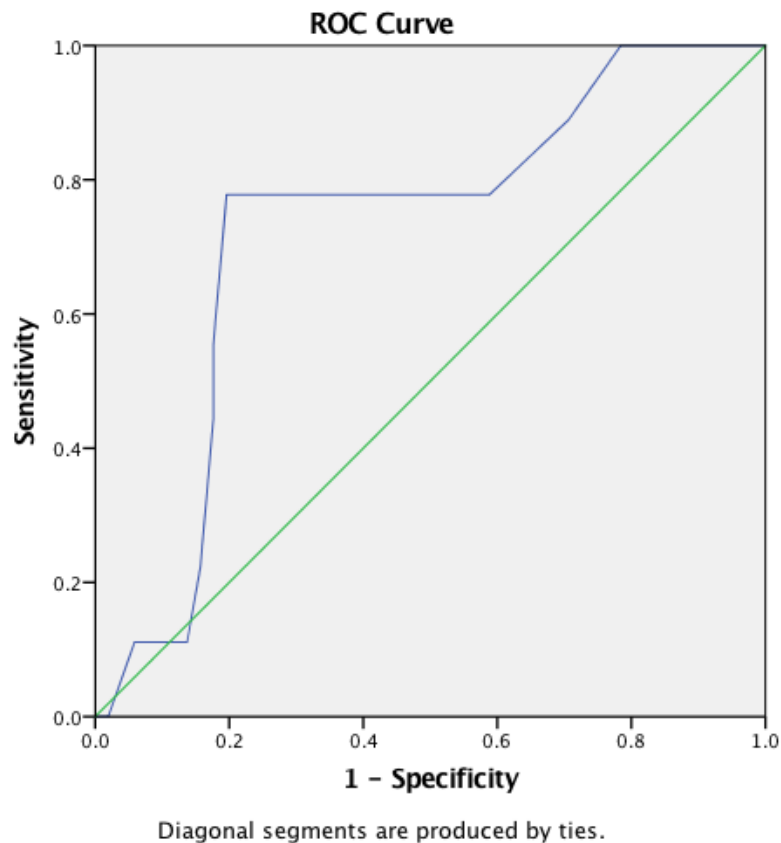


Figure 4.13

ROC curve for pre-operative PainDETECT score.

The AUC for PainDETECT score was 0.727 (95% CI: 0.55, 0.9) ($p=0.031$) indicating that it was significantly better than chance in predicting membership into the ‘poor’ outcome group at 6 months post-TKR surgery (Table 4.88).

Table 4.88: AUC for pre-operative PainDETECT score

Measure	Area	Std. Error	Asymptotic Sig.	Asymptotic 95%CI	
				Lower Bound	Upper Bound
PainDETECT	0.727	0.088	0.031*	0.553	0.9

* Indicates statistical significance at $p \leq 0.05$

A pre-operative PainDETECT score of 11.5 (sensitivity: 0.778, specificity 0.804) gave a positive likelihood ratio of 1.14 for membership into the 'poor' outcome group at 6 months post-TKR surgery. It must be noted that pre-operative PainDETECT was very close to significance ($p=0.052$) in the univariate logistic regression analysis.

Summary of Results

Hypotheses	Accepted/Rejected
1. There will be a difference at pre-operative baseline in QST measures, pain report, functional level, health status, psychological distress and sleep quality between participants categorized as having no to low pain (<4 in NRS pain) versus moderate to severe pain (>4 in NRS pain) at 3 months following TKR surgery.	Partially accepted
2. There will be a difference at pre-operative baseline and at 3 months post-surgery in QST measures, pain report, functional level, health status, psychological distress and sleep quality between participants categorized as showing 'poor' versus 'good' outcomes at 6 months following TKR surgery.	Partially accepted
3. Pre-operative baseline measures (which may include cold pain threshold (CPT), pressure	Accepted

pain threshold (PPT), PainDETECT score, WOMAC score, psychological distress or sleep quality index score) will predict pain levels at 3 months post-TKR surgery.	
4. Pre-operative baseline measures (which may include cold pain threshold (CPT), pressure pain threshold (PPT), PainDETECT score, WOMAC score, psychological distress or sleep quality index score) will predict 'poor' outcome at 6 months post-TKR surgery.	Accepted
5. 3 months post-TKR surgery measures (which may include CPT, PPT, PainDETECT score, surgical approach, immediate post-operative pain intensity or pain catastrophising) will predict 'poor' outcome at 6 months post-TKR surgery.	Accepted
6. Baseline CPT values will predict membership into 'poor' outcome group at 6 months with good sensitivity and specificity.	Rejected
7. Baseline PainDETECT scores will predict membership into 'poor' outcome group at 6 months with good sensitivity and specificity.	Accepted

4.6. Discussion

This study aimed to use a wide range of pre-, peri- and post-operative data from self-report, QST, and medical notes to evaluate the predictors of pain that persists up to 6 months post-TKR surgery.

The present study identified several key measures that predict pain and outcome after TKR surgery. The strongest pre-operative determinants of pain levels at 3 months post-TKR are VDT and PainDETECT. The strongest pre-operative determinants of outcome at 6 months post-TKR are VDT and WOMAC Pain. A search of the current literature failed to turn up any

research on VDT and its predictive value in determining persistent pain post-TKR.

Quantitative Sensory Testing

Pre-operative

The present study reported findings of pre-operative widespread multi-modality sensory impairments (thermal detection thresholds and vibration detection thresholds) in the higher pain group at 3 months and poor outcome group at 6 months post-TKR.

Current QST research has found that OA patients have lower PPTs at both local and distal sites as compared to healthy controls, indicating that OA patients suffer from widespread pain sensitisation (Fingleton et al., 2015; Suokas et al., 2012; Wylde et al., 2012; Wylde et al., 2013).

An ongoing QST study reported PPT as not being a predictor of persistent pain post-TKR at 3 to 4 months post-surgery (Cornelius et al., 2015).

Petersen et al. (2016) investigated the relationship between pre-operative pain mechanisms in knee OA patients and the subsequent amount of pain relief gained at 1 year post-TKR surgery. The investigators reported that the presence of pre-operative widespread pain sensitisation was associated with reduced pain relief at 1 year post-TKR. However, it is important to note that PPT alone was not predictive of post-operative pain relief. The 2 above studies support the findings of this present study.

Wylde et al. (2013) investigated the predictive value of pre-operative QST (PPTs and HPTs) on the likelihood of developing persistent pain post-TKR, and reported that lower pre-operative PPT at a distant site (forearm) is significantly correlated with higher pain levels reported at the operated knee at 1 year post-surgery. This present study did not find any correlation between PPTs and pain levels post-TKR.

Graven-Nielsen et al. (2012) investigated the role of ongoing tissue pathology in the maintenance of enhanced central pain processing in knee OA. The investigators reported that knee OA patients had widespread mechanical hyperalgesia as compared to healthy controls. In this present study, the comparison of PPT was between 2 groups of knee OA patients following TKR surgery. Hence there is no basis for comparison between the studies.

Martinez et al. (2007) reported that pre-operative QST assessment of a small cohort of patients scheduled for TKR showed evidence of localised heat hyperalgesia, which normalized at 4 months after surgery. The present study showed that pre-operatively, patients with higher pain levels at 3 months and poor outcomes at 6 months post-TKR took longer to detect heat changes at the non-operated knee as compared to the lower pain group. However, there was no significant difference in heat detection thresholds at 3 months after the TKR surgery.

Post-operative

There were no significant group differences seen in the QST measures at the post-operative 3 month assessment.

The results of the present study demonstrate that at 3 months post-TKR, there were no significant group differences in the QST measures. This is in line with the results reported by Graven-Nielsen et al. (2012) and Martinez et al. (2007) which showed normalization of the QST results following TKR surgery. However, this directly contradicts the findings of Skou et al. (2013) and Study 1, which reported widespread hyperalgesia in TKR patients who reported significant pain post-surgery.

There are 2 possible explanations for the disparity in results. Both studies by Graven-Nielsen et al. (2012) and Martinez et al. (2007) had small sample sizes. The likelihood of the small sample size in the 2 studies being representative of the entire knee OA population is extremely low. Another explanation is the difference in the assessment time point of the QST testing protocol of this present study and study 1. The present study conducted the QST at 3 months post-TKR, whereas study 1 conducted QST between 12 to 36 months after the TKR surgery. Similarly, Graven-Nielsen et al. (2012) and Martinez et al. (2007) conducted the QST at approximately 4 months post-TKR surgery, whereas Skou et al. (2013) conducted the QST at about 56 months after the revision TKR surgery. Hence it is possible that following TKR surgery, a 'reset' of the neural pathways is triggered due to the removal of the damaged tissue. However, in a small sub-group of patients this 'reset' of the neural pathways is halted or reversed due to the presence of other pain mechanisms.

Neuropathic Pain

Victor et al. (2008) investigated the dimensionality of pain quality using the PQAS and reported a difference in the pain quality of neuropathic versus non-neuropathic pain. The PQAS subscales results of the poor outcome group in this present study reported scores that were higher than the neuropathic pain sample used in the study by Victor et al. (2008).

The significant differences in the levels of self-reported neuropathic pain and pain quality support the QST findings that pre-operatively the nature of pain differs between the groups. The results of this present study support the presence of a neuropathic pain component in a proportion of patients suffering from persistent pain post-TKR. This finding has also been reported in several previous studies (Albayrak et al., 2016; Buvanendran et al., 2010; Fuzier et al., 2015; Harden et al., 2003; Haroutiunian et al., 2013).

Self-Reported Measures

Several studies have investigated the effects of pre-operative pain levels and psychological factors on persistent pain post-TKR surgery. Sullivan et al. (2009) examined the role of psychological factors in predicting pain and disability post-TKR, the results of their study demonstrated that pre-operative pain severity and pain catastrophizing are predictors of post-TKR pain severity at 6 weeks' follow-up.

Brander et al. (2003) conducted a prospective observational study to investigate the natural history of pain following TKR surgery and to identify the predictors of significant persistent pain post-TKR. The investigators reported that the presence of pre-operative depression and anxiety symptoms predicted higher pain levels at 1 year post-TKR. Higher pre-operative pain predicted poor outcome and worse function at 1 year after surgery (Brander et al., 2003).

Duivenvoorden et al. (2013) reported that TKR patients with pre-operative depressive symptoms had worse outcomes at 3 and 12 months following surgery, similar results were also noted in the present study.

Riddle et al. (2010) conducted a prospective cohort study of the effect of psychological status on outcomes after TKR and reported that pain

catastrophizing was a powerful and consistent predictor of poor outcome at 6 months post-TKR.

Judge et al. (2012) investigated the pre-operative predictors of outcomes following TKR surgery and reported that high levels of pain pre-operatively and the presence of pre-operative anxiety/depression predicted poor outcomes at 6 months post-TKR.

The findings of higher levels of pre-operative pain and the presence of psychological distress in the poor outcome group of this present study support the results of the above studies.

The present study found that a higher number of co-morbid conditions is associated with having a poor outcome post-TKR, which supports the results from previous research studies (Escobar et al., 2007; Fitzgerald et al., 2004; Kennedy et al., 2003; Lingard et al., 2004; Mahomed et al., 2002; Wylde et al., 2012). A recent study on diabetic patients with knee OA concluded that the presence of diabetes mellitus significantly increased pain intensity in knee OA (Eitner et al., 2017).

A study investigating sleep disruptions in TKR patients reported that patients who had more post-operative sleep disruptions reported higher pain levels at 1 month post-TKR and reduced function at 3 months post-TKR (Cremeans-Smith et al., 2006). The present study found that TKR patients with higher pain levels at 3 months post-TKR reported significantly reduced sleep quality pre-operatively, and that the poor outcome group at 6 months post-TKR also reported reduced sleep quality at 3 months post-TKR.

Minimal Clinically Important Difference

The minimal clinically important difference (MCID) is defined as the “smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.” (Jaeschke et al., 1989).

Escobar et al. (2007) used the WOMAC and SF-36 questionnaires to establish the MCID in patients undergoing TKR. At 6 months post-TKR, the investigators reported the MCID for WOMAC to be 15 points (ranging from 14 to 22 points); and 10 points (physical domains: ranging from 0.85 to 16 points; mental domains: ranging from -0.32 to 11 points) for the SF-36. In that study, the investigators standardized the WOMAC scores to a range of 0 to 100, with 0 being the best health status and 100 being the worst.

Based on the present study, at 3 months post-TKR the 'no to low pain' group demonstrated scores which are well above the MCID as indicated by Escobar et al. (2007) for all WOMAC domains. The 'moderate to severe pain' group demonstrated scores below the MCID for all domains of the WOMAC. Studies on the efficacy of pharmacological interventions in the treatment of knee OA have reported improvements in the WOMAC score ranging from 36% to 45% (Altman et al., 2007; Babul et al., 2004; Barthel et al., 2009; Kivitz et al., 2008; Williams et al., 2001). Looking at the percentage change in the WOMAC scores at 3 months post-TKR surgery, the 'no to low pain' group demonstrated an average improvement of 54.8% versus the 'moderate to severe pain' group's 32.13% improvement.

The WOMAC results in this present study illustrates that the short-term efficacy and benefits of TKR does not span across the whole spectrum of knee OA patients undertaking a TKR.

Table 4.89 shows the change in the pre-operative mean to post-operative mean of WOMAC scores for this present study. In order to enable a proper comparison, the values in the table have been converted to reflect the same scoring system used by Escobar et al. (2007).

Table 4.89: Change from mean pre-operative to mean post-operative WOMAC scores for 'no to low pain' and 'moderate to severe pain' groups.

WOMAC	'No to Low Pain' Group				Mean Difference	% change
	Pre-Op Mean	SD	Post-Op Mean	SD		
Pain	39.45	16	15.1	15.55	24.35	61.7%
Stiffness	47.63	17.25	30.63	18.63	17	35.69%

Function	39.57	16.54	17.26	14.57	22.31	56.38%
TOTAL	40.22	15.48	18.18	14.6	22.04	54.8%
'Moderate to Severe Pain' Group						
	Pre-Op		Post-Op		Mean	%
WOMAC	Mean	SD	Mean	SD	Difference	change
Pain	59.1	21.25	37.2	17.3	21.9	37.06%
Stiffness	58.13	18.75	49.25	17.38	8.88	15.28%
Function	55.71	17.59	37.5	13.07	18.21	32.69%
TOTAL	56.61	17.7	38.42	13.04	18.19	32.13%

Table 4.90 shows the change in the pre-operative mean to post-operative mean of the SF-36 scores for this present study. In the present study, the 'no to low pain' group reported scores well above the MCID for all the physical domains (PF, RP, BP and GH), and most of the mental health domains (VT, RE and MH). The 'moderate to severe pain' group reported scores above the MCID for most of the physical domains (PF, RP and GH), and only one of the mental health domains (MH).

Table 4.90: Change from mean pre-operative to mean post-operative SF-36 scores for 'no to low pain' and 'moderate to severe pain' groups.

'No to Low Pain' Group						
	Pre-Op		Post-Op		Mean	%
SF-36	Mean	SD	Mean	SD	Difference	change
PF	40.54	24.55	67.81	22.91	27.27	67.26%
RP	52.08	28.18	70.07	26.03	17.99	34.54%
BP	48.75	17.57	68.25	20.4	19.5	40%
GH	78.28	16.71	80.53	15.27	2.25	2.87%
VT	57.13	24.28	64.69	18.05	7.56	13.23%
SF	78.01	25.19	84.43	21.17	6.42	8.23%
RE	75.73	27.47	87.28	19.55	11.55	15.25%
MH	81.84	14.66	84.47	13.01	2.63	3.21%
PCS	38.6	7.77	46.77	8.49	8.17	21.17%
MCS	55.52	10.1	55.93	7.97	0.41	0.74%
'Moderate to Severe Pain' Group						
	Pre-Op		Post-Op		Mean	%
SF-36	Mean	SD	Mean	SD	Difference	change
PF	25	16.96	38.75	20.21	13.75	55%
RP	37.5	27.51	49.61	28.27	12.11	32.29%
BP	32.94	18.82	41.44	15.81	8.5	25.8%
GH	64.65	20.23	70.06	20.46	5.41	8.37%
VT	42.28	20.79	41.8	21.74	-0.48	-1.14%
SF	61.76	28.46	62.5	25.41	0.74	1.2%
RE	68.63	32.48	73.96	24.7	5.33	7.77%
MH	71.18	20.96	73.44	14.46	2.26	3.18%

PCS	32.24	7.65	37.03	8.5	4.79	14.86%
MCS	50.86	13.52	50.31	9.79	-0.55	-1.08%

A longer-term (at 1-2 years) follow-up will shed more light on whether the poor outcome group's WOMAC and SF-36 results will improve over time.

Study Limitations

The limitations of this study must be acknowledged. A wash out of all pain medications prior to testing was not possible due to ethical concerns.

The longitudinal nature of the study meant that an extended length of time was needed to complete the study. This proved to be particularly challenging as at the point of the write up of this thesis, the investigator was not able to complete data collection for all the participants who took part in this present study.

Another limitation of cohort studies is the attrition of participants due to the length of time needed to complete the study, however, only 2 participants were lost at follow-up for this study. The small sample size of this study meant that it is potentially underpowered. Recruitment of participants was adversely affected, due to a change in Western Australia's Public Health funding model. This included the restructuring of RPH (which was the intended primary site of this research project's data collection). The closure of RPH Shenton Park Campus and the subsequent shut down of the RPH Joint Replacement Assessment Clinic were the result of RPH's restructuring process. Another result of the restructure meant that the RPH focus on elective TKR surgery shifted from primary TKRs to complex cases and revisions which are not the intended scope of study for this research project. FHHS was then added as another site of data collection in September 2015. However, participant recruitment proved difficult as only 1 out of every 12 potential TKR patients agreed to take part in the research. 2 orthopaedic surgeons in private practice agreed to collaborate and data collection started in SJOH Hospitals in late June 2016. Due to the above factors, it was impossible to recruit the 120 participants as planned.

Implications

This prospective cohort study identified several predictors of pain and outcome after TKR surgery. By using the predictive models detailed in this present study, it is possible to predict pain levels at 3 months and outcomes at 6 months post-TKR. This study has also identified factors that contribute to the development of persistent pain post-TKR. The results of this study can be used as a basis for a model of risk-stratified care management for knee OA patients who decide to undertake a TKR.

4.7. Conclusion

In conclusion, the present study identified several key pre-operative measures to predict pain levels and outcomes post-TKR surgery. Validation of the predictive models identified in this present study will be needed. Patients who report higher pain levels and poor outcomes after TKR surgery exhibit widespread multi-modality sensory impairments and reduced physical function. They also had significantly higher levels of self-reported pain, neuropathic pain, pain catastrophisation, psychological distress; more co-morbid conditions; and significantly lower scores on the WOMAC and SF-36. Short-term follow-up on this group of patients revealed that even though the TKR surgery improved the WOMAC scores, the level of improvement did not reach the MCID. A longer-term follow-up will help to elucidate the utility and effectiveness of TKR surgery for this group of patients. Brander et al. (2003) reported the prevalence of significant persistent pain to be 18.4% at 6 months and 13.1% at 12 months post-TKR surgery. Wylde et al. (2011) reported that 15% of patients experienced significant pain at 3 to 4 years post-TKR surgery. The present study reported a similar percentage (15%) of patients at 6 months post-TKR having a poor outcome.

Chapter 5

Discussion

The overall purpose of this investigation was to develop a standardised protocol for predicting prior to undertaking a total knee replacement those patients who are likely to develop persistent post-operative pain. The investigation identified several key pre-operative measures which can be used to predict pain levels and outcomes post-TKR surgery.

Complexity of OA pain

Historically, the cause of OA pain was believed to be primarily nociceptive in nature. However, research has shown that there are multiple mechanisms (nociceptive, neuroplastic and neuropathic), pain processes (peripheral and central sensitisation), and psychosocial factors that contribute to the generation of OA pain.

Due to the complexity of OA pain, Suokas et al. (2012) stated “that treatments targeting one specific mechanism may have low efficacy if offered to people whose pain is largely mediated by other mechanisms”. This may be relevant to surgical interventions as well as pharmacological treatments.

Persistent pain post-TKR

The prevalence of persistent pain post-TKR ranges widely from 13.1% to 44% (Baker et al., 2007; Brander et al., 2003; Puolakka et al., 2010; Wylde et al., 2011). This wide variance in the reported prevalence may in part be due to differences in pain levels reported. For example, Wylde et al. (2011) reported that 44% of TKR patients in their study had persistent post-surgical pain at 3 to 4 years post-TKR surgery of any severity, with 15% reporting severe-extreme pain. Brander et al. (2003) reported on “significant pain” post-TKR, finding that 44.4%, 22.6%, 18.4% and 13.1% of their research participants reported this level of pain at 1, 3, 6 and 12 months post-surgery, respectively.

Study 1 (Quantitative Sensory Testing identifies patients with poor outcomes one year following Total Knee Replacement)

Study 1 utilized a cross sectional study design to investigate if there were any differences in QST measures and self-reported measures of pain, health and function between patients who had a good or poor outcome following TKR surgery. A poor outcome was defined as continuing to experience pain more than one year after joint replacement surgery. The study results demonstrated that there were significant differences between the good and poor outcome groups in most of the QST measures (At the knee: PPT, HDT and CPT. At the elbow: PPT, CDT, HDT, CPT and HPT) and self-report questionnaires (PainDETECT, PQAS, EQ-5D and WOMAC). The results of study 1 showed that there were unequivocal differences between patients reporting good and poor outcomes following TKR surgery. The next step from study 1 was to conduct a prospective observational study to investigate if these significant differences were also present pre-operatively.

Study 2 (Sustained cold response)

In study 1, CPT was a QST measure that showed significant differences between the good and poor outcomes groups at both test sites. The results from study 1 showed that CPT and PainDETECT were significantly higher in the poor outcome group. Conventional testing of cold pain response is of limited utility in the clinical setting due to equipment expense and impracticality. Hence, study 2 investigated the reliability and validity of 2 alternative simple methods of testing cold pain response. Study 2 results demonstrated the reliability and validity of both alternative methods of testing cold pain response. The sustained cold response test was chosen as one of the QST measures in study 3 due to its ease of use.

Study 3 (Evaluation of predictors for persistent pain post-Total Knee Replacement)

Study 3 was designed to build on the results and knowledge that was gained from studies 1 and 2. The results from study 3 reported a similar percentage (15%) of patients having significant pain levels at 6 months post-TKR as Brander et al. (2003) and Wylde et al. (2011). This study also demonstrated

that pre-operatively there were significant differences in patients who showed higher pain levels both at 3 months, and at 6 months after TKR surgery. Based on the results of study 1, QST measures such as PPT, HDT and CPT were anticipated to be associated with pain and outcomes following TKR surgery but the results of study 3 proved otherwise. VDT was the only QST measure which demonstrated a significant association to higher pain levels and poor outcomes.

Further analysis revealed that there were a number of pre-operative measures which were found to be predictive of higher pain levels and poor outcome at 3 and 6 months respectively. Several of these measures are of particular interest since they are potentially modifiable. These can be grouped into 4 risk factor categories: psychological distress, neuropathic-type pain, impaired physical function and reduced sleep quality.

Modifiable predictors of persistent pain post-TKR

Psychological distress

Psychological distress has been described as “maladaptive psychological functioning in the face of stressful lifestyle events” (Abeloff et al., 2000). Psychological distress can include post-traumatic stress disorder, depression, anxiety, pain catastrophisation and stress, and is a frequent feature of patients suffering from persistent post-surgical pain (Belfer et al., 2013; Jeffery et al., 2011; Masselin-Dubois et al., 2013; Ross et al., 2015; Skogstad et al., 2014; Vilaro & Shah, 2011; Vincent et al., 2015; Wylde et al., 2011). Hence, it is not unreasonable that it could play a substantial role in the development of persistent pain post-TKR.

A patient in psychological distress can appear to be anxious, be in low mood, having negative beliefs and be unduly worried about their pain.

Several studies have demonstrated that patients presenting with pre-operative psychological distress reported poorer outcomes (e.g. high pain levels, reduced quality of life, poor patient satisfaction) following total knee replacement surgery (Duivenvoorden et al., 2013; Lingard & Riddle, 2007; Masselin-Dubois et al., 2013). However, it is currently unknown whether

individuals develop psychological distress because they are experiencing unexpected and persisting post-surgical pain.

Wade et al. (2011) investigated the role of pain catastrophizing in patients with chronic and severe arthritic pain and suggested that psychological intervention could provide a reduction of pain-related suffering. Psychological intervention such as cognitive-behavioural therapy (CBT) and acceptance and commitment therapy have demonstrated efficacy in treating psychological distress and its influence on pain in a number of conditions (i.e. eating disorders, inflammatory bowel disease, chronic pain) (Bohlmeijer et al., 2011; Darnall et al., 2014; Fledderus et al., 2011; Forman et al., 2007; Hofmann et al., 2012; Lappalainen et al., 2014; Mussell et al., 2003; Powers et al., 2009; Smeets et al., 2006; Swain et al., 2013; Thorn et al., 2007; Wetherell et al., 2011).

Hence, patients who scored highly on the psychological distress risk factor might require a mental health referral and intervention.

Neuropathic-type pain

Phillips et al. (2014) investigated the natural history of neuropathic pain for at least 3 years following TKR surgery. The investigators reported that the incidence of post-operative neuropathic pain was highest at 6 weeks (27% having scores in the intermediate classification of “unclear neuropathic”, and 8% in the “likely neuropathic” classification) and that the number reduced over time to 7% in “unclear neuropathic” and 6% in “likely neuropathic” at their final follow-up (mean of 46 months) (Phillips et al., 2014). This suggests that neuropathic pain following TKR surgery gradually reduces over time. The current series of studies supports this finding. Study 1 demonstrated that TKR patients with a poor outcome at 1 year post-surgery had significantly higher PainDETECT scores (at 12-36 months post-TKR) than the good outcome group. Study 3 showed that pre-operative PainDETECT scores were significantly higher in patients reporting significant pain at 3 months post-TKR surgery; and in the poor outcome group at 6 months post-TKR surgery. In study 3, the poor outcome group also showed significantly higher PainDETECT scores at their 3 months post-surgical assessment. These findings provide support for the current OA-neuropathic pain literature in

showing that: i) a substantial proportion of patients with OA present with features of neuropathic pain; ii) a proportion of patients suffering from persistent pain post-TKR continue to report a neuropathic pain component (Albayrak et al., 2016; Buvanendran et al., 2010; Fuzier et al., 2015; Harden et al., 2003; Haroutiunian et al., 2013).

The results of study 3 demonstrated that pre-operative PainDETECT score was a significant predictor of higher pain levels at 3 months post-TKR. This report of pre-surgical neuropathic pain contradicts Kehlet et al. (2006) who asserted “that postsurgical chronic pain is the consequence either of ongoing inflammation or, much more commonly, a manifestation of neuropathic pain resulting from surgical injury to major peripheral nerves”. Even though the pre-operative PainDETECT score was not a significant predictor of poor outcome at 6 months post-TKR, it was very close to significance. It is anticipated that, with ongoing data collection, as more participants pass the 6 month post-surgery time point, pre-operative PainDETECT will be a significant predictor of persistent pain post-TKR.

It is important to note that in persistent pain post-TKR, the pain may be caused by an abnormal neuromodulatory reaction, rather than the peripheral nociceptive input. Hence, removal of the nociceptive input is less effective as a treatment.

As stated above, there is mounting evidence to suggest that there is a neuropathic pain component in a proportion of patients suffering from persistent pain post-TKR and this phenomenon is identifiable in the OA population pre-operatively using the PainDETECT questionnaire. This suggests therefore that this could be an identifiable and modifiable risk factor.

VDT is a QST measure used for the quantification of large fiber sensory deficits (reduced perception and/or numbness) which has been strongly suggested to be indicative of neuropathic pain (Backonja et al., 2013; Baron et al., 2010). A review on the use of VDT testing in diabetic peripheral neuropathy (DPN) reported good evidence to support its use in the accurate identification of early neuropathic deficits in diabetic patients who are at risk of DPN-associated complications (i.e. foot ulcers) (Garrow & Boulton, 2006).

Kavchak et al. (2012) investigated the relationship between pain and altered somatosensation in individuals with severe knee OA, and reported that VDT was significantly increased as compared to healthy controls. The investigators also reported a moderate correlation between increased VDT and higher levels of perceived instability during a functional task. The results from study 3 demonstrated that patients who had higher pain levels and poor outcomes following TKR surgery had significantly higher VDTs. The presence of hypoesthesia (as measured using VDT) and high scores on the PainDETECT supports the presence of neuropathic-type pain in patients who report poor outcomes post-TKR.

Patients who score highly on the neuropathic-type pain risk factor may benefit from specific pharmacological interventions to address neuropathic pain.

Impaired physical function

Impaired physical function and reduced physical activity levels are hallmark features of individuals suffering from knee OA (Farr et al., 2008; Herbolzheimer et al., 2016; Liikavainio et al., 2008; McAlindon et al., 1993; Sharma et al., 2003). TKR patients with poor outcomes report similar issues with impaired physical function (Baker et al., 2007; Walsh et al., 1998; Wyld et al., 2009). Although potentially this is a pre-operative modifiable feature, impaired function may be influenced by a range of associated factors. For example, is impaired function purely physiological and related to decreased muscle strength or must factors such as pain-related avoidance, or the impact of psychological distress also be considered? Several studies have reported a link between the presence of psychological distress and impaired physical function (Creamer et al., 2000; Ellis et al., 2012; Lingard et al., 2004; Scopaz et al., 2009). Based on the current evidence, impaired physical function might be intrinsically linked with psychological distress. Further studies will be needed to elucidate this association.

In the clinical setting, physical function is measured using physical function tests (i.e. stairs, timed up and go test, timed walking distance tests), knee extensor strength tests (i.e. using handheld dynamometer, isokinetic

machines) and self-report questionnaires (i.e. WOMAC) (Creamer et al., 2000; Fitzgerald et al., 2004; Liikavainio et al., 2008; McAlindon et al., 1993; O'Reilly et al., 1998; Sharma et al., 2003). Patients with impaired physical function can present with poorer performance in physical function tests, reduced knee extensor strength and/or higher scores in the WOMAC physical function scale (indicating increased difficulty in performing functional tasks) (Creamer et al., 2000; Fitzgerald et al., 2004; Liikavainio et al., 2008; McAlindon et al., 1993; O'Reilly et al., 1998; Sharma et al., 2003).

Pre-operative rehabilitation (or prehabilitation) has been described as a “process of enhancing functional capacity of the individual to enable him or her to withstand the stressor of inactivity associated with an orthopaedic procedure” (Ditmyer et al., 2002). Prehabilitation programs usually incorporate components of aerobic, strength, flexibility and functional tasks training (Ditmyer et al., 2002; Topp et al., 2002). Several studies have supported the efficacy of prehabilitation in TKR patients (Brown et al., 2010; Huang et al., 2012; Rooks et al., 2006; Swank et al., 2011; Topp et al., 2009). Huang et al. (2012) investigated the effectiveness of a simple 4 week prehabilitation program in TKR patients and reported that patients in the prehabilitation program had a shorter length of stay in hospital and reduced hospitalization-related expenses as compared to the control group. Rooks et al. (2006) evaluated the effectiveness of a 6 week prehabilitation program on patients who were undertaking a total joint replacement (TKR or THR). The investigators found that those in the prehabilitation program had significantly improved muscle strength as compared to controls, and significantly reduced the risk of admittance into an inpatient rehabilitation facility after surgery. The studies conducted by Rooks et al. (2006) and Huang et al. (2012) showed that following prehabilitation, there was no significant difference in post-operative physical function between groups.

However, the results of several systematic reviews on the efficacy of prehabilitation for TKR were mixed (Kwok et al., 2015; Silkman Baker & McKeon, 2012; Simmons & Smith, 2013). Hence, the idea of prehabilitation is promising but the evidence of its efficacy is still inconclusive. It is important to note that the major limitation to all the current studies on prehabilitation is

the small sample sizes, and that none of the above studies investigated the effects of prehabilitation on fear avoidance and its influence in the development of persistent pain post-TKR.

Patients who scored highly on the impaired physical function risk factor might require a course of prehabilitation with a special focus on modifying fear avoidant behaviour.

Reduced sleep quality

Sleep is complex and generally divided into 2 states, rapid eye movement (REM) sleep and non-REM (NREM) sleep which is further divided into 4 stages (Ancoli-Israel & Ayalon, 2006; Markov & Goldman, 2006). Sleep disorders are classified into primary or secondary (Park et al., 2007). The construct of sleep is very complex and beyond the scope of this doctoral thesis, hence the nature and mechanisms of sleep and its related disorders will not be covered here.

A robust relationship between reduced sleep quality and increased pain levels has been demonstrated in chronic pain conditions as well as in healthy populations (Call-Schmidt & Richardson, 2003; Kundermann et al., 2004; Lautenbacher et al., 2006; Marin et al., 2006; Menefee et al., 2000; Sayar et al., 2002; Schuh-Hofer et al., 2013). However, due to the complexity of both pain and sleep, the true directional relationship between pain and sleep has yet to be elucidated.

Reduced sleep quality has been associated with higher pain levels and increased functional limitations in both knee OA and TKR populations (Creameans-Smith et al., 2006; Hawker et al., 2010; Wilcox et al., 2000; Wylde et al., 2011). Creameans-Smith et al. (2006) reported that TKR patients who had more sleep disturbances had significantly more functional limitations at 3 months following surgery. Wylde et al. (2011) reported that TKR patients who reported more sleep disturbances had significantly higher pain levels than those who slept better. The above studies support the results from study 3 which reported that TKR patients with higher pain levels reported more sleep disturbances.

Treatment of sleep disorders include pharmacological and non-pharmacological interventions. Pharmacological interventions include the use

of hypnotic sedatives, antidepressants and melatonin receptor agonists (Ancoli-Israel & Ayalon, 2006; Gong et al., 2015; Lemoine et al., 2007; Park et al., 2007; Zhu, 2013). Non-pharmacologic treatment of sleep disorders includes sleep hygiene education, CBT, relaxation therapies, sleep assistive devices (i.e. continuous positive air pressure therapy), music therapy and physical exertion (Lai & Good, 2005; Morin et al., 1999; Park et al., 2007; Yang et al., 2012; Zhu, 2013).

Patients who scored highly on the reduced sleep quality risk factor might require a referral to sleep medicine for diagnosis and treatment of their sleep disorder.

Based on the 4 identified risk factors, the tables below (Table 5.1, Table 5.2 and Table 5.3) list the variables that predict pain and poor outcome post-TKR surgery.

Table 5.1: Pre-operative variables predicting 3 month pain levels

		Score	OR	Sensitivity	Specificity
Psychological distress	PCS	1.5			
	Magnification		1.4	0.647	0.649
	PHQ8	4.5	1.19	0.706	0.632
Neuropathic-type pain	PainDETECT	11.5	1.24	0.765	0.877
Impaired physical function	ALF Transfer	10.1	1.14	0.706	0.649
Reduced sleep quality	PSQI Sleep Quality	1.5	3.2	0.529	0.737

Table 5.2: Pre-operative variables predicting 6 month outcomes

		Score	OR	Sensitivity	Specificity
Psychological distress	PCS	2.5			
	Magnification		1.47	0.667	0.784
	PHQ8	7.5	1.28	0.778	0.824

Neuropathic-type pain	PainDETECT	11.5	1.14	0.778	0.804
Impaired physical function	ALF Transfer	11.1	1.16	0.778	0.725

Table 5.3: 3 month post-operative variables predicting 6 month outcomes

		Score	OR	Sensitivity	Specificity
Psychological distress	PCS	0.5			
	Magnification		2.83	0.889	0.863
	PHQ8	6.5	1.4	0.778	0.843
Neuropathic-type pain	PainDETECT	10.5	1.22	0.778	0.824
Reduced sleep quality	PSQI Sleep Quality	1.5	3.03	0.556	0.706

Risk factors

There were a number of variables which were proposed as being pre-operative risk factors in the development of persistent pain post-TKR, see table below (Table 5.4).

Table 5.4: Risk factors for persistent post-surgical pain after TKR.

Risk factors for persistent post-surgical pain after TKR		
Pre-Operative	Intra-Operative	Post-Operative
<ul style="list-style-type: none"> • Age • Female gender • Depression • Anxiety • Pain catastrophising • High levels of pain • Lower functional capacity • Pain sensitivity 	<ul style="list-style-type: none"> • Excessive tissue damage (e.g. Nerves, muscles, soft tissues) • Surgical approach (eg PCL sacrifice, lateral release) 	<ul style="list-style-type: none"> • High levels of acute post-operative pain • Anxiety • Depression • Pain catastrophising • Sleep quality

-
- Presence of comorbid medical conditions
-

Based on Brander et al. (2003); Cremeans-Smith et al. (2006); Elson and Brenkel (2006); Fortin et al. (1999); Hawker et al. (2010); Judge et al. (2012); Lingard et al. (2004); Riddle et al. (2010); Vilaro and Shah (2011); Wilcox et al. (2000) and Wylde et al. (2011)

The results of study 3 did not show age and gender as being predictive of persistent pain post-TKR.

Variables associated with outcomes post-TKR

Table 5.5 below shows some of the variables and their association with outcomes after TKR surgery. Refer to Appendix 6 for detailed results.

Table 5.5: Variables and association with outcomes after TKR.

Variables	Outcomes post-TKR
Smoking history	No association
Duration of pain	No association
Pre-operative medications	Very strong association
Anaesthetic blocks	Moderately strong association
Intra-operative anaesthesia	No association
Surgical approach	No association
Post-operative pain medications	No association
Prosthesis	Moderately strong association
Physiotherapy before TKR	Moderately strong association
Physiotherapy after TKR	No association

Pre-operative medications

Even though the statistical analysis demonstrated a strong association between the type of pre-operative medication and outcomes at 3 and 6 months after TKR surgery, it is difficult to draw any real conclusions or determine the true associations between them. This is mainly due to the numerous combinations of medications (11 combinations of medications)

that were taken by the participants. There may be a trend for those on anti-epileptics and opioids being more likely to have a poor outcome, this could be due to higher levels of pain or hint at an association with neuropathic pain.

Anaesthetic blocks

There was a moderately strong association between type of anaesthetic blocks used and outcomes at 6 months after TKR surgery. However, no definitive conclusion can be reached. 2 members in the poor outcome group received a spinal block for their TKR surgery, compared to none in the good outcome group. This possibly drove the results towards significance. Spinal blocks are typically only used in isolation in patients with more comorbidities, as combination of anaesthetic blocks increases the risks and complications of anaesthesia use.

Prosthesis

Although there appears to be a moderately strong association between type of prosthesis and outcomes at 6 months after TKR surgery, it appears to be driven by 2 types of prosthesis (Nex Gen and Omni Apex) that were used only in the poor outcome group. However, the numbers in the poor outcome group (1 participant received the Nex Gen implant, 1 participant received the Omni Apex implant) are too small to be able to work out a trend.

Physiotherapy before TKR

There was a moderately strong association between physiotherapy treatment before TKR and outcomes at 3 and 6 months after TKR surgery. This may be because pre-operatively, the poor outcome group reported higher levels of pain and functional disability. Hence a greater percentage of the poor outcome group were undergoing pre-operative physiotherapy treatment.

Differences between study 1 and study 3

The results from study 1 showed that there were significant differences between the groups, with the poor outcome group demonstrating widespread mechanical and cold hyperalgesia, sensory changes, lower self-reported health status, impaired physical function and higher levels of neuropathic-

type pain. The results from study 3 did not show any significant group differences in the QST measures (PPT, HDT and CPT) that were anticipated to have associations with pain and outcomes, but there were significant group differences in self-reported health status, sleep quality, psychological distress, co-morbidities and physical function.

There were fundamental differences between study 1 and study 3 which could account for the variances in the results between the 2 studies. These 3 differences are in study design, participant group and assessment time point.

Study design

The 2 studies utilized different study designs. Study 1 utilized a cross sectional study design, whereas study 3 utilized a prospective observational study design.

Participant group

The participant group in study 1 consisted of RPH JRAC patients that were 12-36 months post-TKR surgery. Participants in study 1 were grouped according to the pain component of the KSS. The pain component of the KSS is categorized as no pain (none), mild or occasional pain (stairs only, walking and stairs), moderate pain (occasional, continual), and severe pain (Insall et al., 1989). Participants who had no pain were allocated to the good outcome group, and those with moderate to severe pain were allocated to the poor outcome group. RPH JRAC patients who reported mild or occasional pain were not recruited for the study.

For study 3, participants were recruited pre-operatively from RPH, FHHS and SJOG Subiaco and Murdoch Hospitals. Similarly to study 1, the participants were grouped into a good or poor outcome group based on the pain component of the KSS. Participants who reported no pain and mild or occasional pain were allocated to the good outcome group, and those with moderate to severe pain were allocated to the poor outcome group.

Assessment time point

The assessment time point of the QST testing protocol for the 2 studies was also different. The research assessment for study 1 was performed within 12-

36 months after the TKR surgery, whereas the post-operative research assessment for study 3 was done at 3 months after surgery.

Another possible explanation of the difference in results is that following TKR surgery, a 'reset' of the neural pathways is triggered due to the removal of the damaged tissue. However, in a small sub-group of patients this 'reset' of the neural pathways is halted or reversed due to the presence of other pain mechanisms.

Clinical recommendations

The results of this doctoral research suggest that it may be possible to identify patients who will develop persistent pain post-TKR at the pre-operative consultation with their orthopaedic surgeon.

There would be considerable clinical benefit in developing a battery of measures that could be applied during the initial pre-operative consultation, the results of which could be used to assess patients in terms of modifiable risk factors.

The pre-operative screening tool would need to be short and simple to use, so as not to increase the burden on both clinicians and patients.

This pre-operative screening tool can be used to stratify the risk of developing persistent pain post-TKR. Based on the identified risk factors, patients could then be channeled towards targeted interventions to mitigate the development of persistent pain post-TKR. These interventions might include programs to address psychological distress, pharmacological management of neuropathic pain, programs and medication to improve sleep quality and physical prehabilitation programs. Based on the individual risk profile, an appropriate preparatory program could be developed.

Predicting persistent pain post-TKR

Moving forward, there is some degree of refinement that would be needed before using this pre-operative screening tool in a large multi-centre trial.

The first step towards validation of the screening tool would be to streamline the assessment process. Based on the results of study 3, the assessment

process can be streamlined by cutting out the variables that did not demonstrate statistical significance. The streamlined assessment process can then be applied on knee OA patients who will be undergoing a TKR. The patients who have been identified through this process as likely to have a poor outcome post-TKR, will then need to be followed through to confirm the utility of the tool. The post-surgery (at 3, 6 and 12 months) follow-up screening will be used to check the percentage of patients who were correctly identified as likely to have a poor outcome in the pre-operative assessment and compared against the actual poor outcome numbers.

The second step would be to use the pre-operative screening tool in a large multi-centre trial. Using the results of the screening tool, participants would be allocated to specific targeted interventions (e.g. psychological intervention if results showed that the participant was in psychological distress). The participants would then be reassessed again after the targeted intervention and prior to TKR surgery. The participants would then be followed up post-surgery to determine the efficacy of the targeted intervention in terms of achieving better post-operative outcomes.

The final step would be the development of a computer program/mobile application which could be used by any healthcare professional in predicting persistent pain post-TKR, and directing targeted pre-operative intervention for each patient to ensure good outcomes and maximize the benefits of TKR surgery.

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Appendix 1

painDETECT™		PAIN QUESTIONNAIRE																							
Date:	Patient: Last name: First name:																								
How would you assess your pain now, at this moment?																									
<table border="1"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> <tr> <td colspan="11">none max.</td> </tr> </table>				0	1	2	3	4	5	6	7	8	9	10	none max.										
0	1	2	3	4	5	6	7	8	9	10															
none max.																									
How strong was the strongest pain during the past 4 weeks?																									
<table border="1"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> <tr> <td colspan="11">none max.</td> </tr> </table>				0	1	2	3	4	5	6	7	8	9	10	none max.										
0	1	2	3	4	5	6	7	8	9	10															
none max.																									
How strong was the pain during the past 4 weeks on average?																									
<table border="1"> <tr> <td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td> </tr> <tr> <td colspan="11">none max.</td> </tr> </table>				0	1	2	3	4	5	6	7	8	9	10	none max.										
0	1	2	3	4	5	6	7	8	9	10															
none max.																									
Mark the picture that best describes the course of your pain:																									
		Persistent pain with slight fluctuations <input type="checkbox"/>																							
		Persistent pain with pain attacks <input type="checkbox"/>																							
		Pain attacks without pain between them <input type="checkbox"/>																							
		Pain attacks with pain between them <input type="checkbox"/>																							
Please mark your main area of pain																									
Does your pain radiate to other regions of your body? yes <input type="checkbox"/> no <input type="checkbox"/>																									
If yes, please draw the direction in which the pain radiates.																									
Do you suffer from a burning sensation (e.g., stinging nettles) in the marked areas?																									
never <input type="checkbox"/> hardly noticed <input type="checkbox"/> slightly <input type="checkbox"/> moderately <input type="checkbox"/> strongly <input type="checkbox"/> very strongly <input type="checkbox"/>																									
Do you have a tingling or prickling sensation in the area of your pain (like crawling ants or electrical tingling)?																									
never <input type="checkbox"/> hardly noticed <input type="checkbox"/> slightly <input type="checkbox"/> moderately <input type="checkbox"/> strongly <input type="checkbox"/> very strongly <input type="checkbox"/>																									
Is light touching (clothing, a blanket) in this area painful?																									
never <input type="checkbox"/> hardly noticed <input type="checkbox"/> slightly <input type="checkbox"/> moderately <input type="checkbox"/> strongly <input type="checkbox"/> very strongly <input type="checkbox"/>																									
Do you have sudden pain attacks in the area of your pain, like electric shocks?																									
never <input type="checkbox"/> hardly noticed <input type="checkbox"/> slightly <input type="checkbox"/> moderately <input type="checkbox"/> strongly <input type="checkbox"/> very strongly <input type="checkbox"/>																									
Is cold or heat (bath water) in this area occasionally painful?																									
never <input type="checkbox"/> hardly noticed <input type="checkbox"/> slightly <input type="checkbox"/> moderately <input type="checkbox"/> strongly <input type="checkbox"/> very strongly <input type="checkbox"/>																									
Do you suffer from a sensation of numbness in the areas that you marked?																									
never <input type="checkbox"/> hardly noticed <input type="checkbox"/> slightly <input type="checkbox"/> moderately <input type="checkbox"/> strongly <input type="checkbox"/> very strongly <input type="checkbox"/>																									
Does slight pressure in this area, e.g., with a finger, trigger pain?																									
never <input type="checkbox"/> hardly noticed <input type="checkbox"/> slightly <input type="checkbox"/> moderately <input type="checkbox"/> strongly <input type="checkbox"/> very strongly <input type="checkbox"/>																									
(To be filled out by the physician)																									
<table border="1"> <tr> <td>never</td> <td>hardly noticed</td> <td>slightly</td> <td>moderately</td> <td>strongly</td> <td>very strongly</td> </tr> <tr> <td><input type="checkbox"/> x 0 = 0</td> <td><input type="checkbox"/> x 1 =</td> <td><input type="checkbox"/> x 2 =</td> <td><input type="checkbox"/> x 3 =</td> <td><input type="checkbox"/> x 4 =</td> <td><input type="checkbox"/> x 5 =</td> </tr> </table>				never	hardly noticed	slightly	moderately	strongly	very strongly	<input type="checkbox"/> x 0 = 0	<input type="checkbox"/> x 1 =	<input type="checkbox"/> x 2 =	<input type="checkbox"/> x 3 =	<input type="checkbox"/> x 4 =	<input type="checkbox"/> x 5 =										
never	hardly noticed	slightly	moderately	strongly	very strongly																				
<input type="checkbox"/> x 0 = 0	<input type="checkbox"/> x 1 =	<input type="checkbox"/> x 2 =	<input type="checkbox"/> x 3 =	<input type="checkbox"/> x 4 =	<input type="checkbox"/> x 5 =																				
Total score out of 35																									

Development/Reference: R. Freynhagen, R. Baron, U. Gockel, T.R. Tölle / Curr Med Res Opin, Vol.22, No. 10 (2006)
 painDETECT questionnaire, ©2005 Pfizer Pharma GmbH, used with permission.

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Date: Patient: Last name: First name:

Please transfer the total score from the pain questionnaire:

Total score

Please add up the following numbers, depending on the marked pain behavior pattern and the pain radiation. Then total up the final score:



Persistent pain with slight fluctuations

0



Persistent pain with pain attacks

- 1

if marked, or



Pain attacks without pain between them

+ 1

if marked, or



Pain attacks with pain between them

+ 1

if marked



Radiating pain?

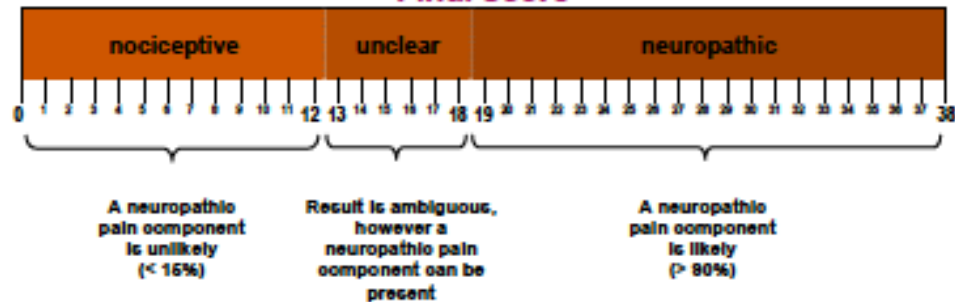
+ 2

if yes

Final score

Screening Result

Final score



This sheet does not replace medical diagnostics.
It is used for screening the presence of a neuropathic pain component.

Development/Reference: R. Freynhagen, R. Baron, U. Giesecke, T.J.L. Tölle / Curr Med Res Opin, Vol.22, No. 16 (2006)

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Appendix 2

Schedule / Timeline for outcome measures

		Pre- operative	1 day post- surgery	At 3 months post- surgery	At 6 months post- surgery
Self-report questionnaires	WOMAC	✓		✓	
	SF-36	✓		✓	
	SCQ	✓		✓	
	PainDETECT	✓		✓	
	PQAS	✓		✓	
	PCS	✓		✓	
	PHQ-8	✓		✓	
	PSQI	✓		✓	
	NRS		✓		
Physical / sensory tests	ROM	✓		✓	
	ALF	✓		✓	
	Knee extensor strength	✓		✓	
	QST	✓		✓	
Knee Society Score	Pain component (telephone interview)				✓

Appendix 3

Data Collection Form 1

Subject ID	
Age	
Gender	
Height (metres)	
Weight (kg)	
Smoking History	
Duration of pain	
Pre-op pain meds	
Anesthesia used in op	
Post-op pain meds	
Prosthesis used	
Surgical approach	

Appendix 4

Data Collection Form 2 (Treatment before TKR)

Participant ID			
Physiotherapy			
Treatment	Details	Number of sessions	Compliance and Efficacy
Hydrotherapy			
Gait training			
Home exercises			
Advice/Education			
EPA			
Other types of intervention			
Treatment	Details	Number of sessions	Compliance and Efficacy

Appendix 5

Data Collection Form 3 (Treatment after TKR)

Participant ID			
Physiotherapy			
Treatment	Details	Number of sessions	Compliance and Efficacy
Hydrotherapy			
Gait training			
Home exercises			
Advice/Education			
EPA			
Other types of intervention			
Treatment	Details	Number of sessions	Compliance and Efficacy

Confounding Variables

- **Age**

There was no significant group difference in age at 3 and 6 months post-surgery (Table A5.1). Therefore, this variable was not included in the logistic regression model.

Table A5.1: Age grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR					
	No to mild pain		Moderate to severe pain		p
	Mean	SEM	Mean	SEM	
Age	70.04	0.96	67.65	1.86	0.257
Outcome group at 6 months post-TKR					
	Good outcome		Poor outcome		p
	Mean	SEM	Mean	SEM	
Age	69.9	1.05	66.56	2.47	0.188

* Indicates statistical significance at $p \leq 0.05$

- **Gender**

Gender as grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.2.

Table A5.2: Gender grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR				
		No to mild pain	Moderate to severe pain	Total
Gender	Male	23	7	30
	Female	34	10	44
	Total	57	17	74
Outcome group at 6 months post-TKR				
		Good outcome	Poor outcome	Total
Gender	Male	21	3	24
	Female	30	6	36

Total	51	9	60
-------	----	---	----

There was no significant association between gender and outcomes at 3 and 6 months post-TKR (Table A5.3)

Table A5.3: Pearson's chi-square tests for gender grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2-sided)
Pain at 3 months	0.004	1	0.951
6 months outcome	0.196	1	0.658

* Indicates statistical significance at $p \leq 0.05$

- **Smoking History**

Smoking history grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.4.

Table A5.4: Smoking history grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR				
		No to mild pain	Moderate to severe pain	Total
Smoking history	Non-smoker	31	10	41
	Ex-smoker	23	6	29
	Smoker	3	1	4
	Total	57	17	74
Outcome group at 6 months post-TKR				
		Good outcome	Poor outcome	Total
Smoking history	Non-smoker	24	7	31
	Ex-smoker	24	1	25
	Smoker	3	1	4
	Total	51	9	60

There was no statistically significant association between smoking history and outcomes at 3 and 6 months post-TKR (Table A5.5).

Table A5.5: Pearson's chi-square tests for smoking history grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2-sided)
Pain at 3 months	0.14	2	0.932
6 months outcome	4.08	2	0.13

* Indicates statistical significance at $p \leq 0.05$

- **Duration of Pain**

There was no significant group difference in duration of pre-operative pain in the index knee at 3 and 6 months post-surgery. Therefore, this variable was not included in the logistic regression model.

Table A5.6: Duration of pain grouped by 3 and 6 months outcome

Pain at 3 months post-TKR					
	No to mild pain		Moderate to severe pain		p
	Mean	SEM	Mean	SEM	
Duration of pain	6.87	0.84	6.29	1.27	
Outcome group at 6 months post-TKR					
	Good outcome		Poor outcome		p
	Mean	SEM	Mean	SEM	
Duration of pain	6.82	0.92	5.61	1.58	

* Indicates statistical significance at $p \leq 0.05$

- **Presence of post-operative infection**

There was only 1 case of deep infection in the operated knee. The participant is recovering well with conservative treatment, and has not reported any pain in the operated knee at 6 months follow-up.

- **Analgesia**

Pre-Operative

Table A5.7 lists the type of pre-operative pain medication taken by participants.

Table A5.7: Pre-operative pain medications grouped by 3 and 6 months outcome

Pre-operative pain medications grouped by pain at 3 months post-TKR				
Medication	Pain <4	%	Pain ≥4	%
None	14	25%	2	12%
Non-Opioid Analgesia	20	35%	5	29%
NSAIDs	6	11%	0	0%
Non-Opioids Analgesia + NSAIDs	7	12%	5	29%
Opioids + Antiepileptics + Corticosteroids	0	0%	1	6%
Non-Opioid Analgesia + Opioids	5	9%	0	0%
Non-Opioid Analgesia + Opioids + Antiepileptics + Tricyclic Antidepressants	1	2%	0	0%
Non-Opioid Analgesia + Opioids + Antiepileptics	0	0%	1	6%
Opioids + NSAIDs + Antiepileptics	0	0%	1	6%
Non-Opioid Analgesia + Opioids + NSAIDs	3	5%	1	6%
Opioids + Benzodiazepines	0	0%	1	6%
Non-opioids + Opioids + Tricyclic Antidepressants	1	2%	0	0%
Total	57	100%	17	100%
Pre-operative pain medications grouped by 6 months outcome post-TKR				

Medication	Good Outcome	%	Poor Outcome	%
None	13	25%	0	0%
Non-Opioid Analgesia	17	33%	2	22%
NSAIDs	6	12%	0	0%
Non-Opioids Analgesia + NSAIDs	7	14%	2	22%
Opioids + Antiepileptics + Corticosteroids	0	0%	1	11%
Non-Opioid Analgesia + Opioids	3	6%	1	11%
Non-Opioid Analgesia + Opioids + Antiepileptics + Tricyclic Antidepressants	1	2%	0	0%
Opioids + NSAIDs + Antiepileptics	0	0%	1	11%
Non-Opioid Analgesia + Opioids + NSAIDs	3	6%	1	11%
Opioids + Benzodiazepines	0	0%	1	11%
Non-opioids + Opioids + Tricyclic Antidepressants	1	2%	0	0%
Total	51	100%	9	100%

There was a statistically significant association between pre-operative pain medication and outcome group at 3 and 6 months post-TKR (Table A5.8). The association was very strong for pain levels at 3 months post-TKR (Cramer's $V=0.53$), and at 6 months post-TKR (Cramer's $V=0.606$).

Table A5.8: Pearson's chi-square tests for pre-operative pain medication grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2-sided)
Pain at 3 months	20.79	11	0.036*
6 months outcome	22	10	0.015*

* Indicates statistical significance at $p \leq 0.05$

Intra-Operative

Anaesthesia used intra-operatively grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.9.

Table A5.9: Anaesthesia used grouped by 3 and 6 months outcome

		Pain levels at 3 months post-TKR		
		No to mild pain	Moderate to severe pain	Total
Anaesthesia	General	20	2	22
	Sedation	37	15	52
	Total	57	17	74
		Outcome group at 6 months post-TKR		
		Good outcome	Poor outcome	Total
Anaesthesia	General	16	1	17
	Sedation	35	8	43
	Total	51	9	60

There was no significant association between intra-operative anaesthesia and outcomes at 3 and 6 months post-TKR (Table A5.10).

Table A5.10: Pearson's chi-square tests for anaesthesia used grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2- sided)
Pain at 3 months	3.41	1	0.065
6 months outcome	1.55	1	0.214

* Indicates statistical significance at $p \leq 0.05$

Anaesthetic blocks used intra-operatively grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.11.

Table A5.11: Anaesthetic blocks grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR				
		No to mild pain	Moderate to severe pain	Total
Anaesthetic blocks	Spinal	2	2	4
	Adductor	7	1	8
	Canal	48	14	62
	Combination	57	17	74
	Total			
Outcome group at 6 months post-TKR				
		Good outcome	Poor outcome	Total
Anaesthesia blocks	Spinal	0	2	2
	Adductor	5	0	5
	Canal	46	7	53
	Combination	51	9	60
	Total			

There was a statistically significant association between anaesthetic blocks and outcome group at 6 months post-TKR (Table A5.12). The association was moderately strong (Cramer's $V=0.454$).

Table A5.12: Pearson's chi-square tests for anaesthetic blocks grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2- sided)
Pain at 3 months	2.15	2	0.341
6 months outcome	12.35	2	0.002*

* Indicates statistical significance at $p \leq 0.05$

Post-Operative

Table A5.13 lists the type of post-operative pain medication taken by participants.

Table A5.13: Post-operative pain medications grouped by 3 and 6 months outcome

Post-operative pain medications grouped by pain at 3 months post-TKR				
Medication	Pain <4	%	Pain >=4	%
Opioid Analgesia	0	0%	1	6%
Non-Opioid Analgesia + Opioids	10	18%	2	12%
Non-Opioid Analgesia + Opioids + Antiepileptics	9	16%	5	29%
Non-Opioid Analgesia + Opioids + NSAIDs	22	39%	3	18%
Non-Opioid Analgesia + Opioids + NSAIDs + Antiepileptics	11	19%	3	18%
Non-Opioid Analgesia + Opioids + NSAIDs + Antiepileptics + Benzodiazepines	1	2%	1	6%
Non-Opioid Analgesia + Opioids + NSAIDs + Benzodiazepines	1	2%	2	12%
Opioids + NSAIDs	1	50%	0	0%
Non-Opioid Analgesia + Opioids + Benzodiazepines	2	4%	0	0%
Total	57	100%	17	100%
Post-operative pain medications grouped by 6 months outcome post-TKR				
Medication	Good Outcome	%	Poor Outcome	%
Opioid Analgesia	1	2%	0	0%
Non-Opioid Analgesia + Opioids	9	18%	1	11%
Non-Opioid Analgesia + Opioids + Antiepileptics	8	16%	2	22%
Non-Opioid Analgesia + Opioids + NSAIDs	17	33%	2	22%

Non-Opioid Analgesia + Opioids + NSAIDS + Antiepileptics	12	24%	2	22%
Non-Opioid Analgesia + Opioids + NSAIDS + Antiepileptics + Benzodiazepines	1	2%	1	11%
Non-Opioid Analgesia + Opioids + NSAIDS + Benzodiazepines	2	4%	1	11%
Opioids + NSAIDS	1	2%	0	0%
Total	51	100%	9	100%

There was no statistically significant association between post-operative analgesia and outcomes at 3 and 6 months post-TKR (Table A5.14).

Table A5.14: Pearson's chi-square tests for post-operative analgesia grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2-sided)
Pain at 3 months	11.58	8	0.171
6 months outcome	3.76	7	0.807

* Indicates statistical significance at $p \leq 0.05$

- **Prosthesis**

Type of prosthesis grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.15.

Table A5.15: Prosthesis grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR		No to mild pain	Moderate to severe pain	Total
Prosthesis	Attune	12	6	18
	Triathlon	32	4	36
	Legion +	12	6	18
	Genesis II			

	Nex Gen	0	1	1
	Omni Apex	1	0	1
	Total	57	17	74
Outcome group at 6 months post-TKR				
		Good outcome	Poor outcome	Total
Prosthesis	Attune	10	3	13
	Triathlon	27	1	28
	Legion + Genesis II	14	3	17
	Nex Gen	0	1	1
	Omni Apex	0	1	1
	Total	51	9	60

There was a statistically significant association between type of prosthesis and outcome group at 6 months post-TKR (Table A5.16). The association was moderately strong (Cramer's $V=0.499$).

Table A5.16: Pearson's chi-square tests for type of prosthesis grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2-sided)
Pain at 3 months	8.7	4	0.069
6 months outcome	14.96	4	0.005*

* Indicates statistical significance at $p \leq 0.05$

- **Surgical Approach**

Surgical approach grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.17.

Table A5.17: Surgical approach grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR

		No to mild pain	Moderate to severe pain	Total
Surgical approach	Medial	55	16	71
	Lateral	2	1	3
	Total	57	17	74
Outcome group at 6 months post-TKR				
		Good outcome	Poor outcome	Total
Surgical approach	Medial	50	8	58
	Lateral	1	1	2
	Total	51	9	60

There was no significant association between surgical approach and outcomes at 3 and 6 months post-TKR (Table A5.18).

Table A5.18: Pearson's chi-square tests for surgical approach grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2- sided)
Pain at 3 months	0.19	1	0.663
6 months outcome	1.99	1	0.159

* Indicates statistical significance at $p \leq 0.05$

- **Treatment**

Before TKR

Physiotherapy treatment (before TKR) grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.19.

Table A5.19: Physiotherapy treatment grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR				
		No to mild pain	Moderate to severe pain	Total
Physiotherapy	No	49	10	59
	Yes	8	7	15

Total		57	17	74
Outcome group at 6 months post-TKR				
		Good outcome	Poor outcome	Total
Physiotherapy	No	44	4	48
	Yes	7	5	12
Total		51	9	60

There was a moderate strength of association between physiotherapy treatment (before TKR) and pain levels at 3 months (Cramer's $V=0.284$) and 6 months (Cramer's $V=0.373$) post-TKR (Table A5.20).

Table A5.20: Pearson's chi-square tests for physiotherapy treatment (before TKR) grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2-sided)
Pain at 3 months	5.97	1	0.015*
6 months outcome	8.37	1	0.004*

* Indicates statistical significance at $p \leq 0.05$

After TKR

Physiotherapy treatment (after TKR) grouped by pain levels at 3 months and outcome at 6 months post-TKR are as shown in table A5.21.

Table A5.21: Physiotherapy treatment (after TKR) grouped by 3 and 6 months outcome

Pain levels at 3 months post-TKR				
		No to mild pain	Moderate to severe pain	Total
Physiotherapy	No	14	4	18
	Yes	43	13	56
Total		57	17	74
Outcome group at 6 months post-TKR				

		Good outcome	Poor outcome	Total
Physiotherapy	No	11	1	12
	Yes	40	8	48
Total		51	9	60

There was no statistically significant association between physiotherapy treatment (after TKR) and pain levels at 3 and 6 months post-TKR (Table A5.22).

Table A5.22: Pearson's chi-square tests for physiotherapy treatment (after TKR) grouped by outcome at 3 and 6 months post-TKR

	Value	df	Asymptotic Significance (2-sided)
Pain at 3 months	0.001	1	0.979
6 months outcome	0.397	1	0.528

* Indicates statistical significance at $p \leq 0.05$

Appendix 7

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)

- Permission to reproduce this questionnaire has been granted by Professor Nicholas Bellamy.

European Quality of Life Questionnaire (EQ-5D)

- Permission to reproduce this questionnaire has been granted by EuroQol.

Self-Administered Comorbidity Questionnaire (SCQ)

- No permission is required to use this questionnaire.

PainDETECT

- No permission is required to use this questionnaire.

Pain Quality Assessment Scale (PQAS)

- Permission to reproduce this questionnaire has been granted by Mapi Research Trust.

Short-Form 36 Health Survey (SF-36)

- Permission to reproduce this questionnaire has been granted by QualityMetric.

Pain Catastrophising Scale (PCS)

- No permission is required to use this questionnaire.

Numeric Rating Scale (NRS)

- No permission is required to use this questionnaire.

Patient Health Questionnaire-8 (PHQ-8)

- No permission is required to use this questionnaire.

Pittsburgh Sleep Quality Index (PSQI)

- Permission to reproduce this questionnaire has been granted by Professor Daniel J. Buysse.

Doctor of Clinical Physiotherapy Portfolio of Work

Candidate:

Kwok Chee Philip Cheong

Student ID:

12558290

Enrolling Area:

School of Physiotherapy and
Exercise Science

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Overview

As stated in the course overview for the Doctor of Clinical Physiotherapy program, “The aims and objectives of the Doctor of Clinical Physiotherapy are to provide high-level clinical practice, inquiry and research skills for senior health professionals, enabling them to evaluate, commission, design, implement and administer research into different aspects of health and to understand the policy implications of such research. The primary aim is to support the emergence of clinical expertise based on a solid foundation of evidence-based practice, clinical reasoning and diagnostic skills.”

I decided to undertake the Doctor of Clinical Physiotherapy program as I felt the need to upgrade my skills and knowledge base in the areas of:

- Musculoskeletal Physiotherapy
- Pain Science
- Clinical Research

The Doctor of Clinical Physiotherapy program offered the perfect fit for my aims as the course structure (which is a combination of coursework and research units) allowed me to tailor the learning to my areas of interest.

I enrolled in the following coursework units, as they enabled me to further my skills and knowledge base in the areas of Pain Science and Musculoskeletal Physiotherapy:

- Management of Pain Disorders 652
 - This unit provides students with current pain knowledge and skills that are applicable to physiotherapists working in the area of musculoskeletal physiotherapy.
- Pharmacology for Health Professionals
 - This unit provides students with a sound knowledge of pharmacological principles and how drugs act on major body systems.

- Physiotherapy Practice 754
 - This unit focuses on the development of advanced level of competency in the clinical management of musculoskeletal disorders.
- Specialised Physiotherapy Clinics
 - This unit allows students to undertake an advanced clinical placement intended to improve their knowledge and skills in a specialised area of clinical practice of their choosing.

As I have completed the Master of Manipulative Therapy course at Curtin University in 2006, I was granted recognition of prior learning for the following units:

- Clinical Anatomy, Pathology and Diagnosis 751
- Clinical Anatomy, Pathology and Diagnosis 752
- Evidence Based Practice 750
- Research Physiotherapy Project 751
- Physiology of Pain 652
- Musculoskeletal Clinical Practice 750
- Musculoskeletal Practice 751
- Functional Rehabilitation 752

My academic record is as shown in the next 2 pages.

The following body of work represents all the assessed pieces of work and records of professional practice for the coursework units that I have undertaken for the degree of Doctor of Clinical Physiotherapy.

This Academic eRecord reflects your results as recorded on the University's student records system.
For an official Academic Transcript, please contact the Student Service Centre.

COURSE CODE COURSE TITLE
314446 Doctor of Clinical Physiotherapy

Recognition of Prior Learning

	Code	Title	Credits	Grade	Mark %
Exemption					
	311902	Musculoskeletal Science 752	25.0		
	311900	Physiotherapy Clinics 752	25.0		
	311901	Physiotherapy Project 652	25.0		
2005					
Semester 1	308274	Clinical Anatomy, Pathology and Diagnosis 751	25.0	6	68
Semester 1	307456	Evidence Based Practice 750	25.0	7	73
Semester 1	308271	Research Physiotherapy Project 751	12.5	8	87
2005					
Semester 2	308272	Clinical Anatomy, Pathology and Diagnosis 752	25.0	6	64
Semester 2	13066	Physiology of Pain 652	12.5	6	65
2006					
Semester 1	308275	Musculoskeletal Clinical Practice 750	12.5	6	63
Semester 1	308276	Musculoskeletal Practice 751	25.0	7	70
2006					
Semester 2	307466	Functional Rehabilitation 752	12.5	5	59
Total Credits			225.0		

Completed Within the Course

	Code	Title	Credits	Grade	Mark %
2013					
Semester 1	314443	Physiotherapy Dissertation Preparation 750	100.0	PASS	
2013					
Semester 2	314444	Physiotherapy Dissertation 751	100.0	PASS	
2014					
Semester 1	312204	Physiotherapy Practice 754	25.0	7	77
2014					
Semester 2	311903	Management of Pain Disorders 652	25.0	8	81
2015					
Semester 1	PHRM5002	Pharmacology for Health Professionals	25.0	7	78
2016					
Semester 1	PHTY7012	Specialised Physiotherapy Clinics	25.0	PASS	

Kwok Chee Philip Cheong 12558290

Date of Issue: 6 December 2016

This Academic eRecord reflects your results as recorded on the University's student records system.
For an official Academic Transcript, please contact the Student Service Centre.

Total Credits **525.0**

ACADEMIC STATUS

Good Standing

Course Weighted Average

72.00

Note:

Academic transcripts printed on or after 28 February 2006 include designated credit and automatic credit in the calculation of the CWA. Transcripts printed prior to this date do not.

From 2015 Codes and some Titles have changed. New alpha numeric codes have replaced existing numeric codes (Course, Major, Stream, Unit and Thesis). Students may have a combination of old and new codes and/or unit titles on their Academic Record.

..... **End of Record 12558290**

Kwok Chee Philip Cheong 12558290

Date of Issue: 6 December 2016

Chapter 1: Physiotherapy Practice 754

1.1 Introduction

This unit focused on the development of an advanced level of theoretical and clinical specialised competency in clinical management of musculoskeletal disorders. Emphasis is placed on advanced clinical reasoning of complex clinical cases and synthesis of ethical and professional issues relevant to advanced musculoskeletal clinical practice. The contact time for this unit was 39 hours.

1.2 Syllabus

- Advanced clinical practice assessment and management in an area of specialized practice.
- Examination of contemporary evidence for best clinical practice.
- Presentation of complex cases.
- Discussion of topics related to specialist clinical practice.

1.3 Learning Outcomes

1. Demonstrate an advanced level of theoretical and clinical specialised competency in clinical examination and management in a specialised area of clinical practice.
2. Integrate an advanced clinical reasoning framework related to the assessment and management of patients in a specialised area of clinical practice.
3. Demonstrate an advanced level of specialised clinical knowledge in the management of patients in a specialist area of clinical practice.
4. Evaluate the issues and levels of evidence for the efficacy of physiotherapy approaches when managing patients in a specialist area of clinical practice or evaluate professional and ethical issues relevant to physiotherapy practice in a specialist area.

1.4 Assessments

The work handed in for assessment in this unit were:

1.4.1 Clinical Masterclass Case Presentation

- For this assignment, I had to nominate a musculoskeletal disorder of specific expertise / interest to myself. The brief is that I have been invited to present this session at an upcoming professional conference as a 2-hour practical workshop. As an expert in my field, the conference wishes to provide attendees with a state of the art update that assists clinicians with the translation of current evidence into their daily clinical practice. The task is to present to the group a “Masterclass Clinical Update” on my chosen topic.
- The topic I had chosen was, “Bacterial infection as a cause of low back pain”.

1.4.2 Seminar Presentation

- For this assignment, I had to nominate a professional practice topic of interest to myself and my target audience. The brief is that I have been invited by Musculoskeletal Physiotherapy Australia (MPA) to present a 40 minute seminar (with 20 minutes of discussion time after) on my chosen topic. The MPA has commenced this series of seminars to update its members on professional practice issues relevant to clinicians.
- The topic I had chosen was, “Interpretation of MRI for lumbar spine”.

1.4.3 Specialist Topic Paper

- For this assignment, I had to nominate a clinical or professional practice topic of interest to myself and my target audience. The brief is that I have been commissioned by the Medical Journal of Australia to write a “Perspectives” article for their journal on my chosen specialist topic. This is an opportunity to influence the perception of advanced musculoskeletal physiotherapy practice in the wider general medical community (my target audience).
- The topic I had chosen was, “Persistent pain post-total knee replacement: Still an enigma”.

1.4.1 Clinical Masterclass Case Presentation

1.4.1 Clinical Masterclass Case Presentation

BACTERIAL INFECTION AS A CAUSE OF LOW BACK PAIN

PHILIP CHEONG, FAMEI
APA MUSCULOSKELETAL PHYSIOTHERAPIST

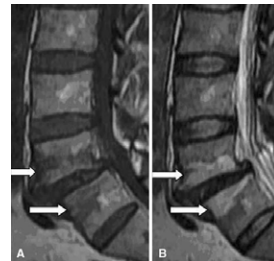
OUTLINE

- **Modic changes**
 - Types
 - Mechanisms
- **Article review**
 - Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae?
 - Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy

MODIC CHANGES (TYPES)

- **Type 1**
 - Bone marrow edema and inflammation
 - Strong association with NSLBP (Toyone et al., 1994; Mitra et al., 2004; Kjaer et al., 2006; Albert & Manniche, 2007; Kuusma et al., 2007; Modic, 2007)
 - Prevalence rate of 15-29% (Mitra et al., 2004; Kjaer et al., 2006; Albert & Manniche, 2007)
- **Type 2**
 - Conversion of normal red bone marrow to yellow fatty marrow
- **Type 3**
 - Subchondral bone sclerosis

MODIC CHANGES (TYPE 1)



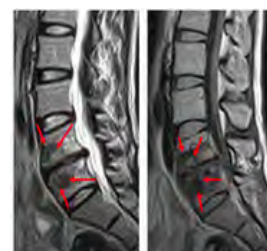
Zhang et al. (2008). Modic changes: a systematic review. *Eur Spine J.* 17, 1289-1299

MODIC CHANGES (TYPE 2)



Zhang et al. (2008). Modic changes: a systematic review. *Eur Spine J.* 17, 1289-1299

MODIC CHANGES (TYPE 3)



http://www.mskmedical.com/modic_en/what_are_modic_changes_en/

1.4.1 Clinical Masterclass Case Presentation

MODIC CHANGES (MECHANISMS)

- Biomechanical
 - Endplates – 'weak link'
 - Fissures/microfractures
- Biochemical
 - Upregulation of inflammatory mediators in the nucleus pulposus
 - Disc herniation is the entry point of anaerobic bacteria

Zhang et al. (2008). Modic changes: a systematic review. *Eur Spine J.* 17, 1289-1299

BACTERIAL INFECTION OF NUCLEAR TISSUE

- Aims:
 - To investigate if herniated nucleus material from Lx disc herniations is infected with bacteria
 - To determine if patients with an anaerobic infected disc are more likely to develop MCs following a disc herniation as compared to patients with sterile discs or aerobic infections

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

- Primary surgery for Lx disc herniation
 - Inclusion criteria
 - Between 18-65 years old
 - MRI confirmed Lx disc herniation
 - Immunocompetent
 - No antibiotic Rx within previous 2/52
 - No previous epidural or back surgery

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

- Method
 - 5 biopsies performed on each subject
 - Stringent antiseptic protocols
 - New set of sterile instruments with each biopsy
 - Cultures
 - All 5 tissue samples incubated under aerobic and anaerobic conditions for 7 days at 37 °C

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

- Method
 - MRI at baseline and 1-2 years after surgery

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

- Results
 - 28 (46%) out of 61 subjects had +ve cultures
 - 26 (43%) had +ve anaerobic cultures
 - 4 (7%) had 2 bacteria strains present
 - 2 (3%) had +ve aerobic cultures

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

1.4.1 Clinical Masterclass Case Presentation

BACTERIAL INFECTION OF NUCLEAR TISSUE

Table 1 The distribution of bacteria in the positive cultures

Isolated microorganisms	Herniated discs (N = 61)	Of the herniated discs with positive microbiology (N = 28)
Anaerobic		
<i>Propionibacterium acnes</i>	24 (40 %)	86 %
Cocci-negative staphylococci	2 (3 %)	7 %
Aerobic		
Gram-positive cocci (1 single)	4 (6 %) ^a	14 % ^a
Gram-negative rod (1 single)	1 (1.5 %)	3 %
<i>Neisseria</i> species	1 (1.5 %) ^b	3 % ^b
Positive cultures	32 % (46 %) ^c	113 % ^d

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

• Results

- +ve aerobic cultures
 - None developed new MCs
- +ve anaerobic cultures
 - 20 (80%) out of 25 subjects developed new MCs
- -ve cultures
 - 15 (44%) out of 34 subjects developed new MCs

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

Table 2 Contingency table for the association between anaerobic culture and new Modic changes

	New MCs at the site of the disc herniation	No new MCs	Totals
Positive anaerobic culture	20	5	25
Pure aerobic culture	0	2	2
Negative culture	15	19	34
Totals	35	26	61

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

• Results

- +ve anaerobic cultures is strongly associated with development of new MCs
 - OR of 5.60 (95% CI 1.51-21.95)

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

• Discussion

- Confirmed findings with 5 previous studies of bacteria found in extruded nuclear material
 - *P. acnes*
- *P. acnes* thrive in areas of low vascularity and low pH
- Why do the patients with -ve cultures develop MC?

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

BACTERIAL INFECTION OF NUCLEAR TISSUE

• Conclusion

- Occurrence of MC Type 1 due to edema surrounding an infected disc
- Discs infected with anaerobic bacteria significantly more likely to develop MCs

Albert et al. (2013) Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? *Eur Spine J.* 22, 690-696

1.4.1 Clinical Masterclass Case Presentation

THOUGHTS/QUERIES/CONCERNS

- ?Difference in numbers reported for +ve anaerobic cultures
- Contamination of sample

PROPIONIBACTERIUM ACNES

- Infection after RC repair (Settecerri et al., 1999; Herrera et al., 2002)
- Endocarditis (Lazar & Schulman, 1992; Mohsen et al., 2001)
- Corneal infections (Underdahl et al., 2000)
- Postop endophthalmitis (Clark et al., 1999)
- Focal intracranial infections (Chu et al., 2001)
- CSF shunt infections (Thompson & Albright, 1998)
- Sciatica (Stirling et al., 2001)
- Prosthetic joint infections (Yu et al., 1997; Tunney et al., 1999)

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Aim
 - Test the efficacy of Modic antibiotic spine therapy (MAST) in patients with chronic LBP, new Modic type 1 changes in the vertebrae adjacent to a previously herniated disc
 - Investigate whether a dose-response relationship could be identified

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J, 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Inclusion criteria
 - Between 18-65 years old
 - MRI confirmed Lx disc herniation
 - L3/L4 or L4/L5 or L5/S1
 - Within preceding 6-24 months
 - LBP > 6/12
 - Both conservative and surgically treated patients included
 - Repeat MRI showed MC type 1 adjacent to the previously herniated disc

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J, 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Exclusion criteria
 - Allergy to antibiotics
 - Current pregnancy or lactation
 - Kidney disease
 - Pending litigation

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J, 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Treatment protocol
 - Amoxicillin-Clavulanate (500mg/125mg) (Bioclavid®)
 - 3 x daily
 - 8 hr intervals
 - 100 days

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J, 22, 697-707

1.4.1 Clinical Masterclass Case Presentation

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Randomization (Computer-generated)
 - A (n=45)
 - 1 Bioclavid tablet
 - B (n=36)
 - 1 placebo tablet
 - C (n=45)
 - 2 Bioclavid tablet
 - D (n=36)
 - 2 placebo tablet

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J*, 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

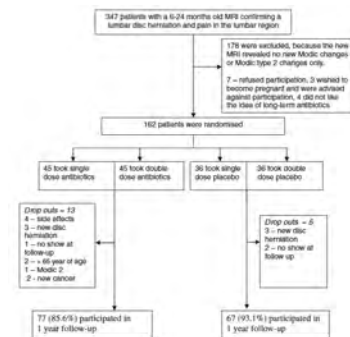
- Primary outcome measures
 - Roland Morris Disability Questionnaire (RMDQ)
 - LBP Pain Rating Scale

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J*, 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Secondary outcome measures
 - Global perceived effect
 - Leg pain
 - Hours with LBP during the last 4/52
 - EQ-5D Thermometer
 - Day with sick leave
 - Bothersomeness
 - Constant pain
 - MRI Modic grading
 - Serum analysis

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J*, 22, 697-707



ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Results
 - Antibiotic group

	Baseline	100 days	1 Year
RMDQ	15.0	11.5	7.0
Back pain	6.7	5.0	3.7
Leg pain	5.3	3.0	1.7

- Placebo group

	Baseline	100 days	1 Year
RMDQ	15.0	14.0	14.0
Back pain	6.3	6.3	6.3
Leg pain	4.0	4.3	4.3

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J*, 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Results
 - Antibiotic group

	Baseline	100 days	1 Year
Back pain (Hrs)	448	180	64
Sick days	51.0	-	18.9
EQ-5D	59	65	75

- Placebo group

	Baseline	100 days	1 Year
Back pain (Hrs)	448	200	448
Sick days	42.0	-	45.4
EQ-5D	60	60	60

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. *Eur Spine J*, 22, 697-707

1.4.1 Clinical Masterclass Case Presentation

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Discussion
 - Statistically & clinically significant improvement in all outcome measures
 - Improvement seen at 1 year compared to at end of treatment
 - Propionic acid
 - Reduction of leg pain

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J. 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Discussion

	Antibiotic baseline n = 90	Antibiotic 1-year follow-up n = 77	Placebo baseline n = 72	Placebo 1-year follow-up n = 67
Had low back pain	100 %	67.5 %	100 %	94.0 %
Had constant pain	75.3 %	19.5 %	73.1 %	67.2 %
Had disturbed sleep at night due to pain	74.0 %	29.9 %	76.1 %	61.2 %

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J. 22, 697-707

ANTIBIOTIC RX IN PATIENTS WITH MC TYPE 1

- Conclusion
 - Antibiotics as a treatment option:
 - LBP > 6/12
 - MC type 1 in the adjacent vertebrae following a previous disc herniation
 - Up to 2 years
 - All other treatment options has failed

Albert et al. (2013) Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy. Eur Spine J. 22, 697-707

THOUGHTS/QUERIES/CONCERNS

- Difference between single dose and double dose antibiotics
- Conflict of interest
 - MAST (Modic Antibiotic Spine Therapy) Medical™
- Other tests to determine bacterial infection
- Duration of antibiotic therapy

TAKE HOME MESSAGE

- Antibiotic Rx may be highly effective treatment in a specific sub group of patients with LBP
- Study needs to be replicated and further tested

Questions?

Thank you for your time
and attention

1.4.2 Seminar Presentation

1.4.2 Seminar Presentation

INTERPRETATION OF MRI FOR LUMBAR SPINE

PHILIP CHEONG, APAM, FAMEI
APA MUSCULOSKELETAL PHYSIOTHERAPIST
CLINICAL DOCTORATE CANDIDATE (CURTIN)

OBJECTIVES

- Know the indications for when to order MRI investigations for low back pain
- Knowledge of the current evidence for lumbar spine MRIs
- Interpret MRI of the lumbar spine relevant to physiotherapy practice
- Determine if the results of the MRI fits the patient's clinical picture

OUTLINE

- MRI basics
- Indications for use of MRI
- Summary of current evidence
- MRI costs
- MRI & reporting epidemiology
- Iatrogenic effects of early MRI
- Common sequences for musculoskeletal MRI
- MRI images
- Case studies

MAGNETIC RESONANCE IMAGING (MRI)

- 3 planes of imaging
 - Axial, Coronal, Sagittal
- Optimal for soft tissue
 - Disc, muscle, ligament and spinal cord/nerve roots
- Variable Sequences
- No ionizing radiation

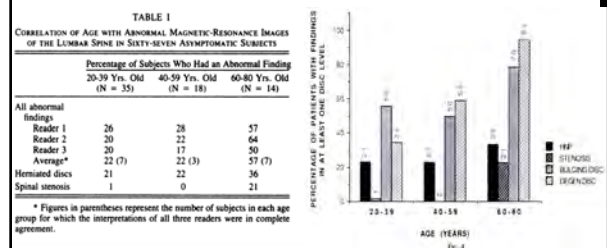
WHEN IS IT INDICATED?

Imaging Action	Rationale
Immediate	<ul style="list-style-type: none">• Risk factors for spinal infection• Risk factors for/or signs of cauda equina syndrome• Severe neurologic deficits
Defer imaging after a trial of therapy	<ul style="list-style-type: none">• Signs & Symptoms of radiculopathy• Risk factors for/or symptoms of spinal stenosis
No Imaging	<ul style="list-style-type: none">• No criteria for immediate imaging• Back pain improved or resolved after a 1/12 trial of therapy• Previous spinal imaging with no change in clinical status

Chou et al. (2011) Diagnostic imaging for LBP: Advice for High-Value Health Care from the American College of Physicians. Ann Intern Med, 154, 181-189

SUMMARY OF CURRENT EVIDENCE

- Abnormal findings common in asymptomatic population (Boden et al., 1990)



1.4.2 Seminar Presentation

SUMMARY OF CURRENT EVIDENCE

- Abnormal findings common in asymptomatic population (Jensen et al., 1994)

Table 1. Prevalence of Bulges, Protrusions, and Extrusions on MRI Scans in 98 Asymptomatic Subjects and 27 Symptomatic Subjects.*

	BULGE		PROTRUSION		EXTRUSION	
	no. of subjects (%)					
Evaluator 1						
Asymptomatic subjects	52	(53)	30	(31)	2	(2)
Symptomatic subjects	23	(85)	14	(52)	8	(30)
Evaluator 2						
Asymptomatic subjects	50	(51)	23	(23)	0	
Symptomatic subjects	18	(67)	15	(56)	6	(22)
Average of the two evaluators						
Asymptomatic subjects	51	(52)	26.5	(27)	1	(1)
Symptomatic subjects	20.5	(76)	14.5	(54)	7	(26)

*Bulge, protrusion, and extrusion are defined in the Methods section.

SUMMARY OF CURRENT EVIDENCE

- Abnormal findings common in asymptomatic population (Jarvick et al., 2001)

Table 4. Prevalence [no. (%)] of Imaging Findings by Lumbar Spine Level

Imaging Finding	Lumbar Spine Level					Overall*	
	L1-L2	L2-L3	L3-L4	L4-L5	L5-S1	Any†	Protruded
Disc degeneration	55 (37)	62 (42)	81 (55)	99 (67)	108 (72)	134 (81)	98 (62)
Disc extrusion (moderate or severe)	44 (30)	58 (39)	69 (47)	78 (53)	95 (64)	122 (83)	91 (60)
Loss of disc height	21 (14)	14 (10)	20 (14)	41 (28)	44 (30)	82 (54)	60 (39)
Bulge	26 (18)	26 (18)	48 (32)	70 (47)	54 (37)	95 (64)	69 (45)
Protrusion	3 (2)	9 (6)	12 (8)	18 (12)	28 (20)	48 (32)	37 (25)
Extrusion	0 (0)	0 (0)	1 (1)	4 (3)	5 (3)	9 (6)	5 (3)
Nerve root compromise	0 (0)	0 (0)	0 (0)	1 (1)	4 (3)	5 (3)	3 (2)
Annular tear	4 (3)	7 (5)	15 (10)	26 (18)	30 (20)	56 (38)	45 (30)
Endplate changes	6 (4)	9 (6)	10 (7)	14 (10)	19 (13)	29 (20)	24 (16)
Stenosis (moderate or severe)	0 (0)	4 (3)	4 (3)	6 (4)	4 (3)	15 (10)	7 (5)
Facet degeneration (moderate or severe)	0 (0)	3 (2)	4 (3)	16 (11)	9 (6)	27 (18)	19 (13)

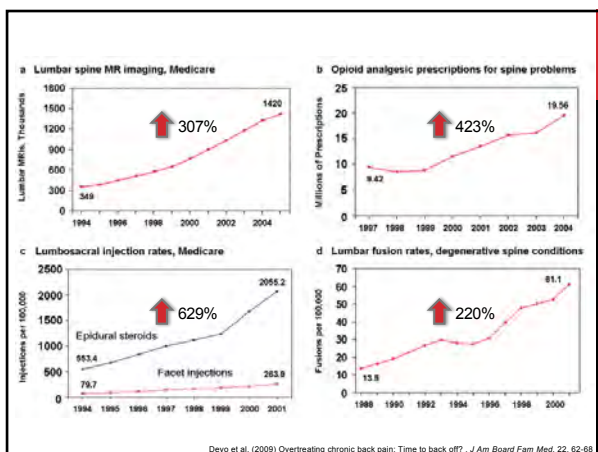
* Present at one or more levels.
† All subjects in cohort.
‡ Those subjects with modified Roland = 0; pain frequency score = 4; pain bothersomeness score = 4 in = 100.
§ χ^2 test: $P < 0.05$.

SUMMARY OF CURRENT EVIDENCE

- The degree of abnormal findings in MRI \neq pain and/or disability (Berg et al., 2013)
- Not predictive of development or duration of pain (Borenstein et al., 2001)
- Interpretation of MRI varies between readers (Boden et al., 1990)

SUMMARY OF CURRENT EVIDENCE

- Strong association between rates of advanced spinal imaging and spinal surgery (Verrilli & Welch, 1996; Lurie et al., 2003; Jarvick et al., 2003; Webster et al., 2013)
- Rates of interventional procedures (i.e. epidural steroid, facet joint injections) increased $>3x$ (Friedly et al., 2007)



MRI COSTS

- USA Medicare population (Parker et al., 2008)
 - MSK imaging increased 25.7% from 1996 to 2005
 - MSK MRI has increased 353.5% from 1996 to 2005
 - Projected MSK imaging costs in 2020 - \$3.6 billion
 - MSK MRI - \$2.0 billion

1.4.2 Seminar Presentation

MRI COSTS

- Appropriateness of MRI requests (Emery et al., 2013)

Table. Appropriateness of Requests for Magnetic Resonance Imaging (MRI)

Category	No. (%)		
	Appropriate	Uncertain	Inappropriate
Lumbar spine total	443 of 1000 (44.3)	272 of 1000 (27.2)	285 of 1000 (28.5)
Specific indication			
Acute back pain, ≤6 wk	9 of 39 (23.1)	6 of 39 (15.4)	24 of 39 (61.5)
Chronic back pain, >6 wk	36 of 213 (16.9)	78 of 213 (36.6)	99 of 213 (46.5)
Radiculopathy	70 of 296 (23.6)	122 of 296 (41.2)	104 of 296 (35.1)
Claudication	21 of 107 (19.6)	58 of 107 (54.2)	28 of 107 (26.2)
Postoperative back or leg pain	160 of 167 (95.8)	0 of 167	7 of 167 (4.2)
Ordering physician			
Neurologist	27 of 56 (48.2)	18 of 56 (32.1)	11 of 56 (19.6)
Neurosurgeon	112 of 148 (75.7)	21 of 148 (14.2)	15 of 148 (10.1)
Orthopedic surgeon	36 of 73 (49.3)	21 of 73 (28.8)	16 of 73 (21.9)
Family physician	207 of 611 (33.9)	186 of 611 (30.4)	218 of 611 (35.7)
Other	61 of 112 (54.5)	28 of 112 (23.2)	23 of 112 (20.3)

MRI & REPORTING EPIDEMIOLOGY

Comment: The following findings are so common in people without low back pain that while we report their presence, they must be interpreted with caution and in the context of the clinical situation. (Reference –Jarvik et al, Spine 2001)

Findings: (prevalence in patients without low back pain), Disk degeneration (decreased T2 signal, height loss, bulge) (91%), Disk T2—signal loss (83%), Disk height loss (56%), Disk bulge (64%), Disk protrusion (32%), Annular tear (38%)

McCullogh et al., 2012

MRI & REPORTING EPIDEMIOLOGY

- 237 Lx MRI reports
 - 71 (30%) included the statement
 - 166 (70%) did not include the statement
- Statement group
 - Less likely to receive prescription for narcotics
 - Repeat cross-sectional imaging and physio referral also less common
- Similar rates of steroid injections, surgical consultations and surgeries between groups

McCullogh et al., 2012

IATROGENIC EFFECTS OF EARLY MRI

- More likely to have surgery compared to those who had x-rays with no difference in outcomes (Jarvik et al., 2003)
- Longer disability duration (Graves et al., 2012)
- Webster et al. (2013) reported:

	Radiculopathy		Non-specific LBP	
	No-MRI (n=45)	Early-MRI (n=178)	No-MRI (n=209)	Early-MRI (n=123)
Disability (Days)	50	184	44.4	165
Total medical costs (US \$)	4,100	22,339	2,306	17,028

MAGNETIC RESONANCE IMAGING (MRI)

Common Sequences

- T1 - weighted
- T2 - weighted
- STIR



<http://www.neuroradiologycases.com/2011/08/post-radiotherapy-marrow-changes.html>

1.4.2 Seminar Presentation

MAGNETIC RESONANCE IMAGING (MRI)

T1 (BRIGHT)

- Fat
- Marrow
- Slow-flowing blood
- Proteinaceous tissue
- Paramagnetic contrast agents

T1 (DARK)

- Air
- Bone
- Fast-flowing blood
- Water

MAGNETIC RESONANCE IMAGING (MRI)

T2 (BRIGHT)

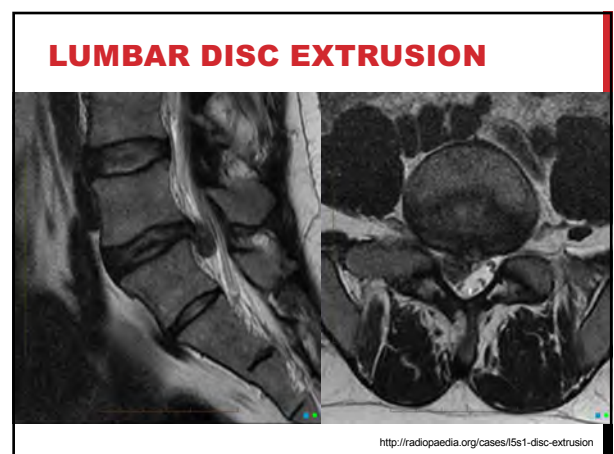
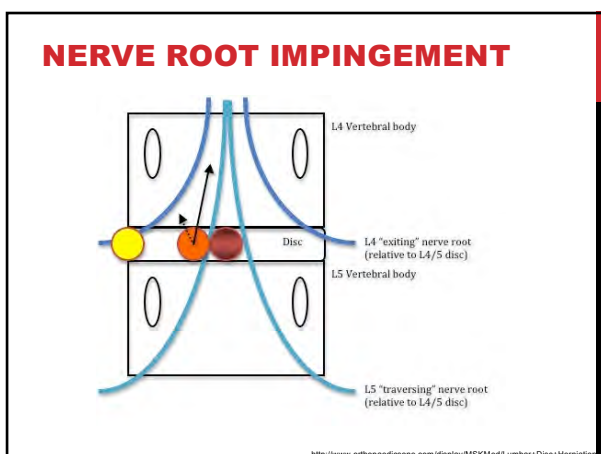
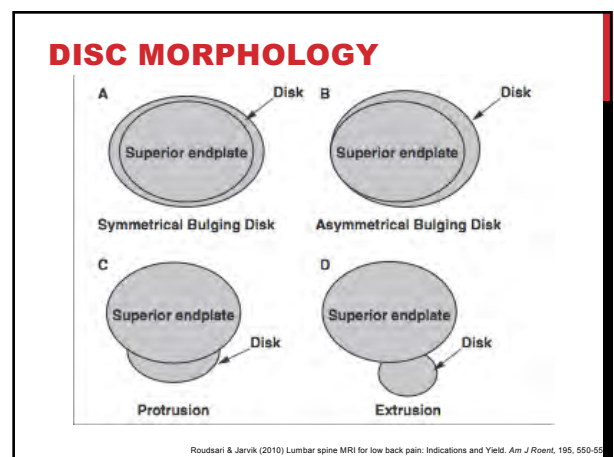
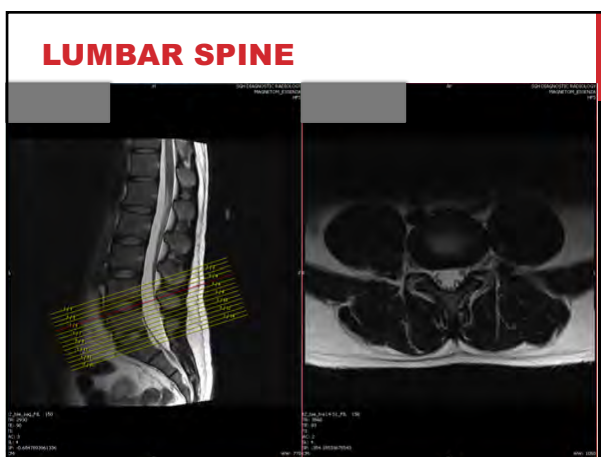
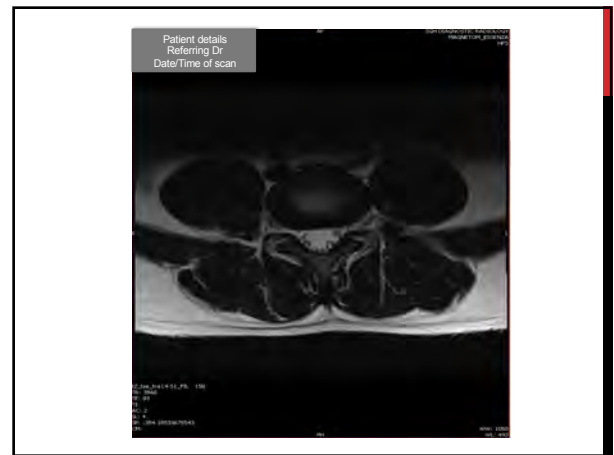
- Fat
- Marrow
- CSF
- Water
- IVD
- Proteinaceous tissue

T2 (DARK)

- Air
- Bone
- Fast-flowing blood

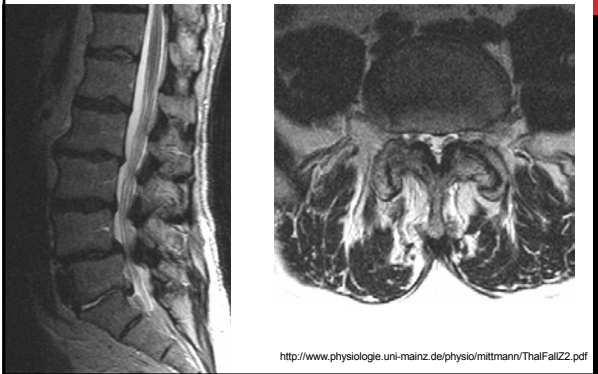


1.4.2 Seminar Presentation

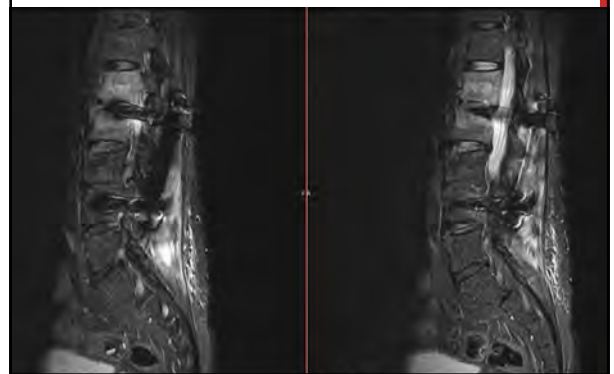


1.4.2 Seminar Presentation

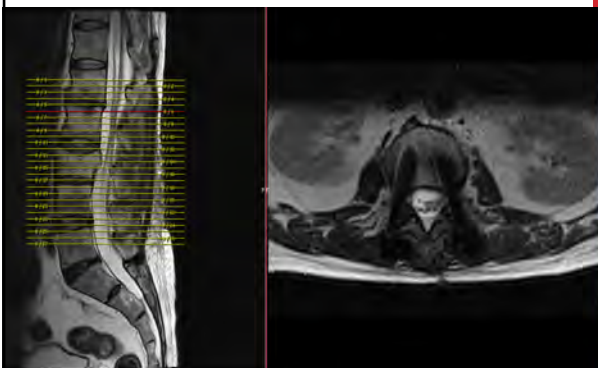
SPINAL STENOSIS



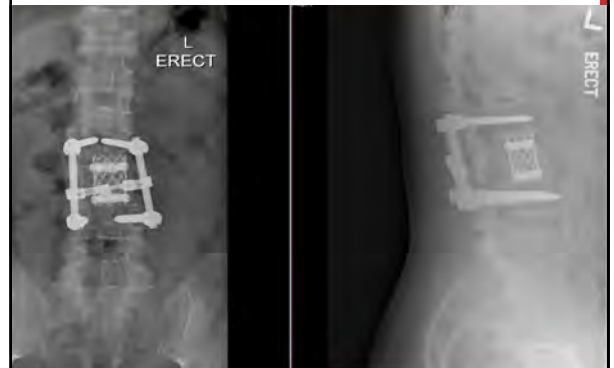
SPINAL INSTRUMENTATION



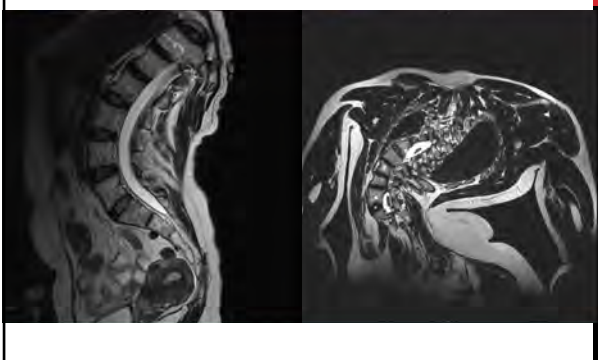
SPINAL INSTRUMENTATION



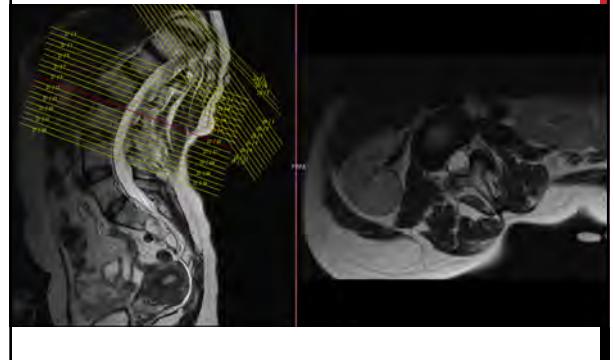
SPINAL INSTRUMENTATION (X-RAY)



SCOLIOSIS

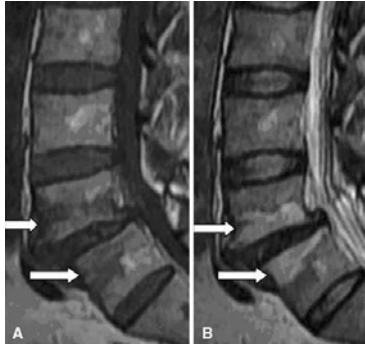


SCOLIOSIS



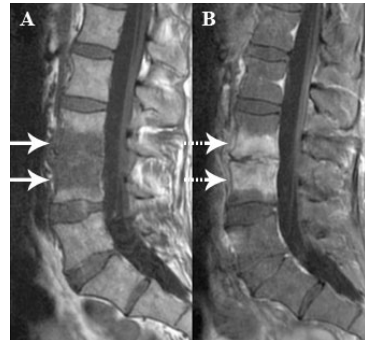
1.4.2 Seminar Presentation

MODIC CHANGES (TYPE 1)



Zhang et al. (2008). Modic changes: a systematic review. *Eur Spine J.* 17, 1289-1299

LUMBAR DISCITIS



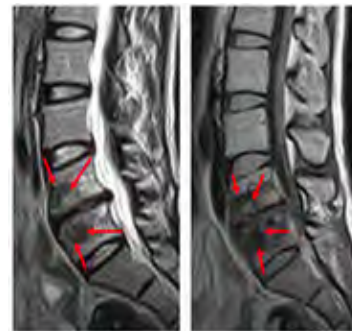
http://www.mghradrounds.org/index.php?src=gendocs&link=nov_dec_2006

MODIC CHANGES (TYPE 2)



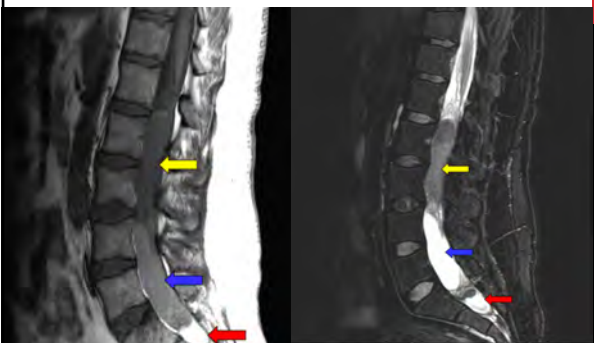
Zhang et al. (2008). Modic changes: a systematic review. *Eur Spine J.* 17, 1289-1299

MODIC CHANGES (TYPE 3)



http://www.mastmedical.com/modic_en/what_are_modic_changes_en/

TUMOUR



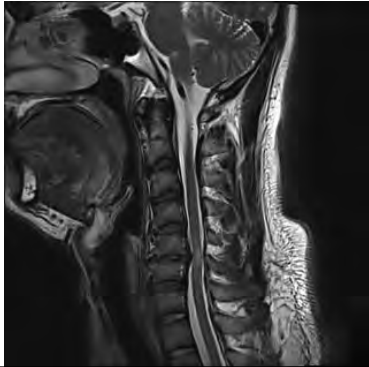
<http://radiology.casereports.net/index.php/rcr/article/viewarticle/42181>

SPINAL METASTASIS



1.4.2 Seminar Presentation

CORD CHANGES

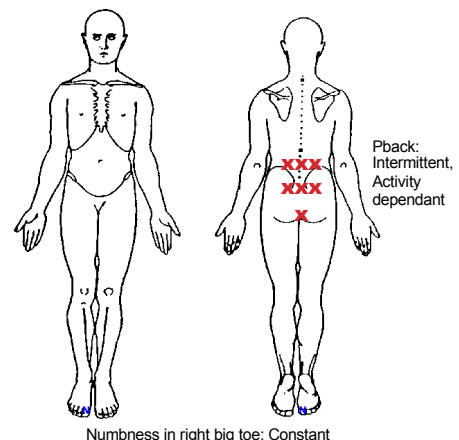


CASE STUDY 1

- 43 year old, male
- More than 18/12 history of low back pain. Also c/o constant numbness in right big toe for many years.
- Back pain started after doing heavy lifting at work.

CASE STUDY 1

- Aggravating activities:
 - Bending over, immediate pain, pain scale 7/10
 - Lifting, immediate pain, pain scale 7/10
- Similar history of back pain 10 years ago for which he received physiotherapy treatment (Traction, Electrical Stimulation, McKenzie Extension exercises).



PHYSICAL EXAMINATION

- Lx Flexion: $\frac{1}{2}$ ROM, pain reproduced
- Lx Extension: FROM
- No loss of strength
- Reflexes normal
- Slight loss of light touch sensation in right big toe
- Motion palpation: L5/S1 hypo in flexion

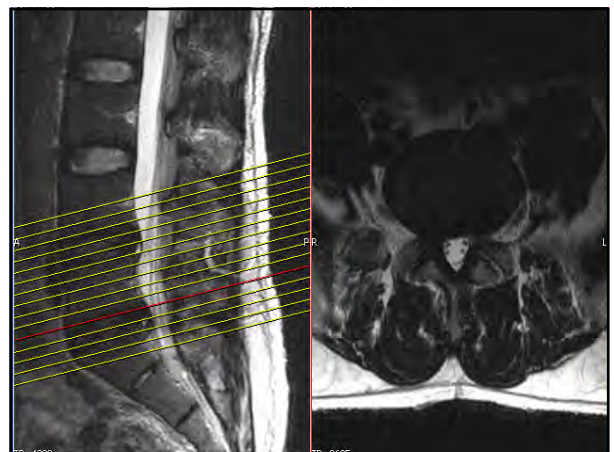
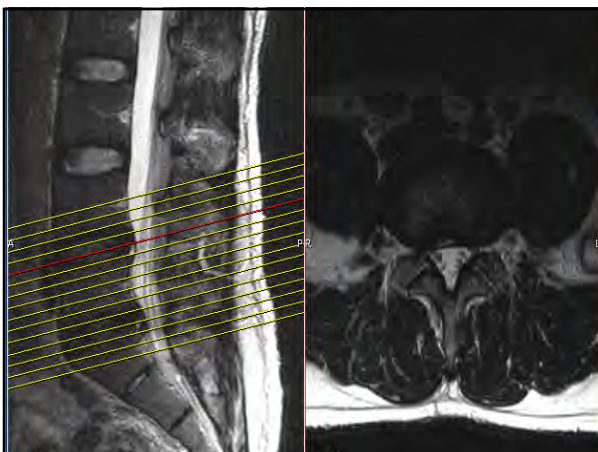
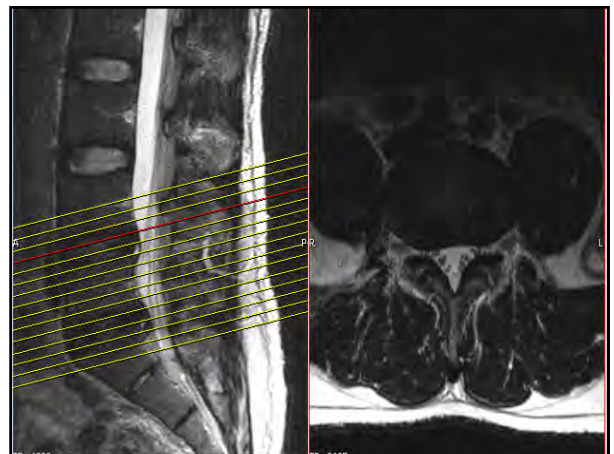
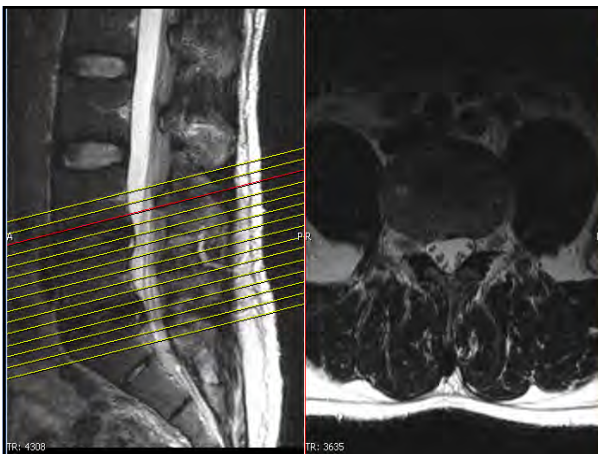
PHYSICAL EXAMINATION

- Palpation: Increase tone in Lx Extensors, and tender on palpation
- SIJ cleared
- Neurodynamics testing
 - Slump test, L=R=✓✓
 - SLR, L=R=✓✓

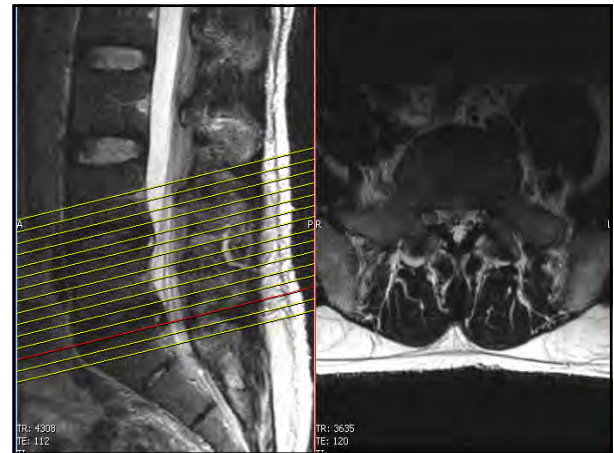
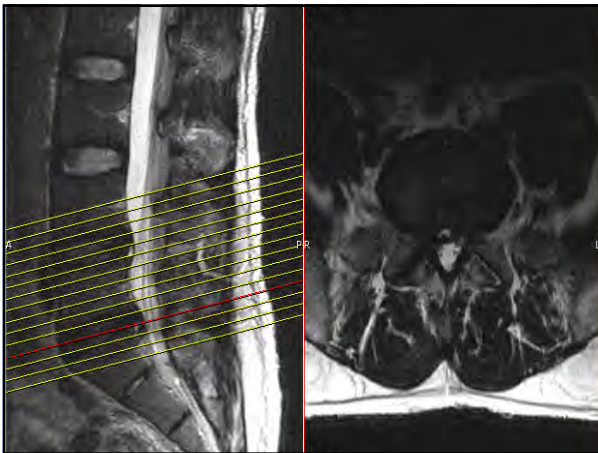
1.4.2 Seminar Presentation

MRI

- Indication for MRI?



1.4.2 Seminar Presentation



MRI

- What are the main findings on the MRI?
- Do the MRI findings correlate to the clinical assessment?

TREATMENT

- Dx: NSCLBP, Movt impairment disorder – flexion pattern
- Education
- Home Exercise Program
 - Knee to chest, Posterior pelvic tilts, Seated Lx flexion
- Soft tissue release for Lx Extensors.
- Had 5 sessions of therapy, and no longer has back pain.

CASE STUDY 2

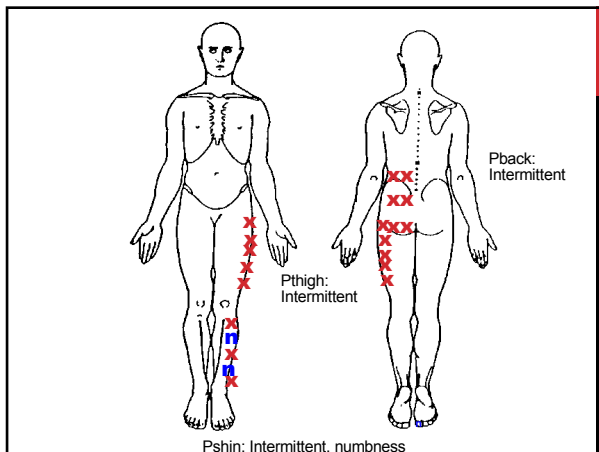
- 19 year old, male
- 2/52 history of worsening severe left sided buttock, posterolateral thigh, lateral shin pain with numbness
- Recently enlisted into armed forces, and has been doing a lot of running when the pain started

Courtesy of Ms Liang Zhiqi
Senior Physiotherapist, SGH

CASE STUDY 2

- Presented into ED, unable to FWB on left leg
- Aggravating activities:
 - FWB on left leg, pain scale 9/10 & numbness worsened
 - Lx AROM, pain scale 9/10

1.4.2 Seminar Presentation



PHYSICAL EXAMINATION

- Lx AROM: $\frac{1}{4}$ ROM, pain and numbness reproduced
- No loss of strength
- Reflexes normal
- Decreased sensation in left lateral lower leg
- Neurodynamics testing
 - SLR, L= 30 deg, reproduced leg symptoms, SLR, R=✓✓

MRI

- Indication for MRI?



1.4.2 Seminar Presentation



MRI

- What are the main findings on the MRI?
- Do the MRI findings correlate to the clinical assessment?

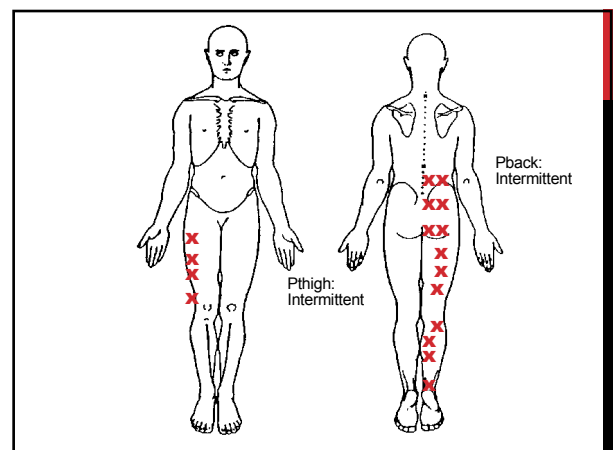
CASE STUDY 3

- 38 year old, female
- 8/52 post partum.
- 3-4 year history of right sided low back, buttock, posterior thigh and calf pain.
- Pain has worsened since giving birth

Courtesy of Ms Irene Toh
Principal Physiotherapist, SGH

CASE STUDY 3

- Aggravating activities:
 - Lx Flexion, pain scale 8/10
 - Sustained sitting for >10 mins, pain scale 8/10
- Relieving factors:
 - Lying supine, eases completely in 5 mins
 - Standing, eases to 2/10



1.4.2 Seminar Presentation

PHYSICAL EXAMINATION

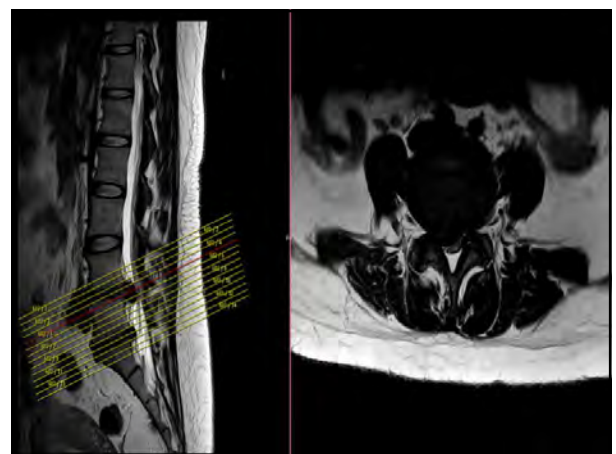
- Lx flexion: $\frac{1}{2}$ ROM, pain reproduced
- Myotomes
 - L4
 - L= 5/5, R= 4/5
 - L5
 - L=5/5, R= 4/5
- Reflexes
 - Knee
 - L=R= diminished
 - Achilles
 - L=R= diminished

PHYSICAL EXAMINATION

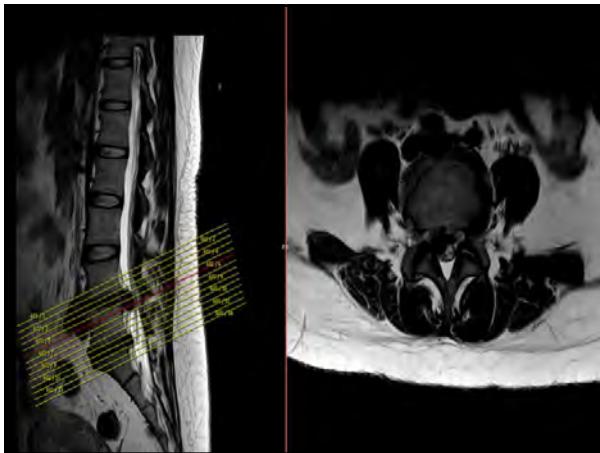
- Sensation intact
- Neurodynamics testing
 - SLR
 - L= $\checkmark\checkmark$, R= 30 deg, reproduced leg symptoms
 - Slump
 - L= $\checkmark\checkmark$, R= +ve

MRI

- Indication for MRI?



1.4.2 Seminar Presentation



MRI

- What are the main findings on the MRI?
- Do the MRI findings correlate to the clinical assessment?

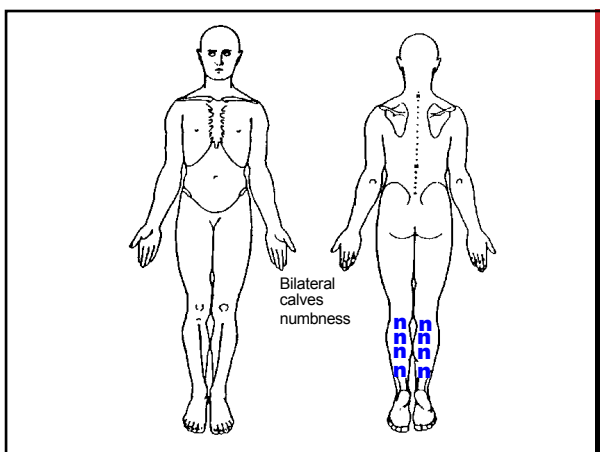
CASE STUDY 4

- 86 year old, male
- Bilateral decompression laminectomy in 2012 – No improvement
- Bilateral calves numbness with walking for 3-4 mins
- Has difficulty with urination

Courtesy of Ms Irene Toh
Principal Physiotherapist, SGH

CASE STUDY 4

- Aggravating activities:
 - Walking for 3-4 mins, bilateral leg numbness
- Relieving factors:
 - Lying supine



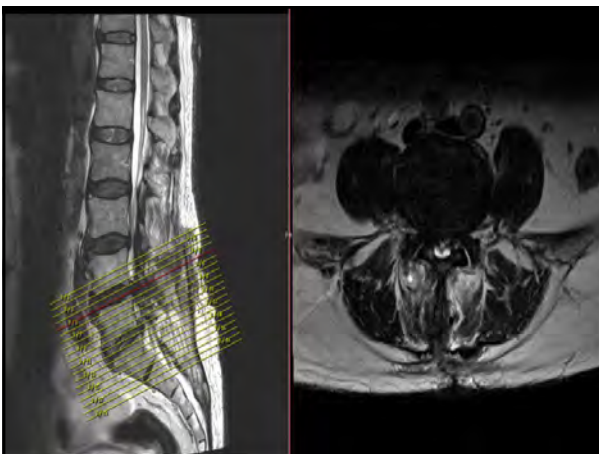
PHYSICAL EXAMINATION

- Lx flexion: FROM
- No loss of strength
- Sensation intact
- Reflexes
 - Knee
 - L=R= diminished
 - Achilles
 - L=R= diminished

1.4.2 Seminar Presentation

MRI

- Indication for MRI?

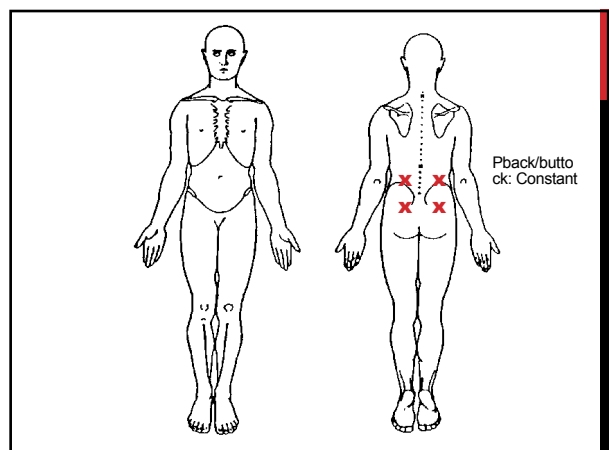


MRI

- What are the main findings on the MRI?
- Do the MRI findings correlate to the clinical assessment?

CASE STUDY 5

- 79 year old, male
- c/o bilateral leg weakness following a fall x 2/7 ago
- Slipped and landed on bottom
- Slight pain in bottom and lower back



1.4.2 Seminar Presentation

PHYSICAL EXAMINATION

- Lx flexion: FROM
- No loss of strength
- Sensation intact
- Reflexes
 - Knee
 - L=R= ✓✓
 - Achilles
 - L=R= ✓✓

MRI

- Indication for MRI?



MRI

- What are the main findings on the MRI?
- Do the MRI findings correlate to the clinical assessment?

TAKE HOME MESSAGE

- A diagnosis that is based on magnetic resonance imaging, in the absence of objective clinical findings, may not be the cause of the patient's pain, and an attempt at operative correction could be the first step towards disaster (Boden et al., 1990)

Questions?

**Thank you for your time
and attention**

Additional images



1.4.2 Seminar Presentation



1.4.2 Seminar Presentation



1.4.3 Specialist Topic Paper

Persistent pain post-total knee replacement: Still an enigma.

“Introline”

20% of post-TKR patients report severe chronic pain. How much do we actually know about this condition?

Osteoarthritis

The 2011-2012 Australian Health Survey showed that 14.8% (around 3.3 million) of Australians suffer from arthritis, with a higher prevalence in females (17.7%) compared to males (11.8%).¹ 55.9% of Australians who had arthritis reported that they suffered from osteoarthritis (OA).¹

In the past, OA pain was attributed only to joint damage (nociceptive pain mechanism), and the resulting inflammatory response (neuroplastic pain mechanism) in the OA damaged joint. However, recent advances in pain sciences research have shown that OA pain is much more complex. Nociceptive, neuroplastic and neuropathic pain mechanisms, in combination with psychological and social factors (e.g. pain catastrophising, depression, anxiety, lack of social support, lower socioeconomic status) have been shown to contribute to the generation of OA pain.²

The knee joint is commonly affected by OA, and the presentation of pain in knee OA sufferers varies greatly; from localised activity-related pain to referred or even widespread pain at sites distant from the knee.^{3,4}

Due to this variability in pain presentation, it has been hypothesized that both peripheral and central pain processes may be active to varying degrees in patients with knee OA.³ Peripheral and central sensitisation of the pain pathways usually results in normal stimuli becoming painful. Peripheral sensitization is likely to be driven by inflammation of the damaged structures in the OA joint, whereas central sensitization may be driven by the continuous intense nociceptive input from the OA joint.³

However, removal of the nociceptive input does not mean that central sensitisation is eliminated.⁴

Even with recent advances that have led to improved understanding of OA pain, its pathophysiology is complex and still not fully understood. In summary, there are multiple mechanisms (nociceptive pain, neuroplastic pain and neuropathic pain), pain processes (peripheral sensitization, central sensitization), and psychological/social factors that contribute to the generation of OA pain.^{2,4} To further complicate the nature of OA pain; the mechanisms, pain processes and factors that mediate OA pain vary among individuals.^{2,4}

Management of knee OA is generally based on symptom severity and range from:

- (i) Non-pharmacological interventions (e.g. Weight reduction, Lifestyle modification, Exercise rehabilitation)
- (ii) Pharmacological interventions (e.g. NSAIDS, Analgesics – Opioid / Non-opioid, Viscosupplements)
- (iii) Surgical interventions (e.g. Arthroscopy, Total knee replacement) when both non-pharmacological and pharmacological interventions have failed.

Total knee replacement

Total knee replacement (TKR) is a surgical procedure commonly used to manage chronic knee pain and improve physical function in those with advanced knee OA. Knee OA is the most common diagnosis for TKR surgery, accounting for 97.4% of all TKR surgeries in Australia.⁵ In 2012, a total of 41,810 TKR surgeries were performed in Australia,⁵ at a cost ranging from \$18,874 to \$23,702 per surgery in a public hospital.⁶ Similar to other developed nations, TKR surgery is on the rise in Australia. From 2003 to 2012, the numbers of TKR surgery have increased by a staggering 92.4%.⁵

Although many patients report good outcomes (reduced pain and increased function) a proportion of patients continue to report significant and persistent pain following TKR. A recent systematic review on the prevalence of persistent pain post-TKR have reported that about 20% of patients continue to report severe chronic pain after a technically successful and uncomplicated TKR.⁷

Persistent post-surgical pain

Persistent post-surgical pain has been defined by the International Association for the Study of Pain to be pain that has developed after surgery, has been present for at least 3 months, and is independent of any pre-existing pain condition.⁸

Current belief of persistent post-surgical pain: 'New' pain after TKR

The current belief is that persistent post-surgical pain is the consequence of ongoing inflammation (from intra-operative damage), or a manifestation of neuropathic pain resulting from the surgical intervention (due to surgical damage to nerves).⁹

Risk Factors

The risk factors for development of persistent pain post-TKR are well documented in the research literature.⁹ The table below summarizes the main proposed factors.

Table 1: Risk factors for persistent post-surgical pain after TKR.⁹

Risk factors for persistent post-surgical pain after TKR		
Pre-Operative	Intra-Operative	Post-Operative
<ul style="list-style-type: none"> • Genetic predisposition • Female gender • Depression • Anxiety • Pain catastrophising • High levels of pain • Long history of pain 	<ul style="list-style-type: none"> • Excessive tissue damage (e.g. Nerves, muscles, soft tissues) • Surgical approach (e.g. Posterior cruciate ligament sacrifice + lateral release) • Ongoing inflammatory response 	<ul style="list-style-type: none"> • High levels of acute post-operative pain • Anxiety • Depression • Pain catastrophising

Even though the risk factors are well documented, there is currently no way of discerning which individuals are genetically predisposed to developing persistent post-TKR pain. It is also not possible to refuse TKR surgery to patients just because of their gender; and as TKR surgery is advocated only for end stage knee OA, most patients will have a relatively long history of pain with high pain levels.

Hence, the knowledge of these factors has yet to mitigate the risk of TKR patients developing persistent pain post-surgery.

Causes of persistent pain post-TKR

From a structural point of view, it has been proposed that the causes of pain after TKR fit into 3 categories: intra-articular biomechanical, intra-articular biological and extra-articular; however, the occurrence rates of these causes of pain after TKR are very low.¹⁰ Hence, it appears that for a substantial number of TKR patients there is no clear, structural cause for their persistent post-surgical pain.

Several groups have attempted to categorize persistent post-TKR pain in order to better manage poor outcomes. The UK-based Support and Treatment After Replacement (STAR) Expert Group (<http://www.bristol.ac.uk/clinical-sciences/research/musculoskeletal/orthopaedic/research/star>), based at the University of Bristol involves pain researchers from across Europe, Canada and Australia, has proposed 5 relatively distinct post-operative presentations (personal communication from Prof Anthony Wright, member of STAR Expert Group). These are neuropathic pain, painful instability, proximal tibial tenderness, patellofemoral pain and chronic pain syndromes (i.e. widespread pain sensitisation and complex regional pain syndrome).

The premise of TKR surgery is to remove the damaged joint and replace it with artificial components; however, this only removes the nociceptive and inflammatory pain mechanisms (stemming from the damaged OA joint) that drive OA pain.

Due to the complexities of OA pain, treatments for OA (such as TKR) that target only one specific mechanism will not be effective for patients whose pain is largely mediated by other mechanisms.⁴ This could explain the seemingly high rates of persistent pain post-TKR.

Widespread pain sensitivity before TKR: Pre-existing pain conditions

Recent research (using quantitative sensory testing techniques) on knee OA patients without any other diagnosed pre-existing chronic pain conditions have found that a proportion of these patients have widespread pain sensitization.¹¹ This finding is of interest, as widespread pain sensitisation has been associated with the development of persistent pain post-TKR.¹¹ However, there is a possibility that the widespread pain sensitization is due to central sensitivity as a result of OA pain.

Further research needs to be done on this area in order for us to gain more understanding on the nature of the widespread pain sensitivity and its contribution to the development of persistent pain post-TKR.

Persistent pain post-TKR: Pre-existing pain versus 'new' pain

When looking at all the available literature on persistent pain post-TKR, it is possible that persistent pain post-TKR may reflect 'new' pain resulting from the surgical intervention, or may reflect lack of success in the detection/resolution of pre-existing pain conditions.

In order to better understand the nature of persistent pain post-TKR and to differentiate between unresolved pre-operative pain and newly-developed post-operative pain, it has been suggested that an ideal future study would therefore need to include pre- and post-operative psychological and neurophysiological assessment, detailed intra-operative data and detailed post-operative pain data.⁹ There is currently no study of this quality available.

Greater clarity is needed about the relative roles of:

- (i) Pre-existing pain conditions and
- (ii) Newly acquired pain post-surgery, in persistent pain post-TKR.

Moving forwards

Based on the number of TKR operations in 2012, and the reported rates of persistent pain post-TKR, it can be postulated that the cost of the failed surgery alone ranged from \$157.8 million to \$198.1 million in 2012. There is an urgent need to conduct more research on persistent pain post-TKR just on the basis of the above financial figures.

Physiotherapists are perfectly placed to lead the research push towards increasing understanding of persistent pain post-TKR. This is due to their training and advanced knowledge of pain sciences and anatomy, as well as their roles in conservative treatment of patients with knee OA, pre-operative assessment and post-operative rehabilitation of TKR patients.

The main focus of future research should be on the development of a screening protocol that will identify patients who are likely to experience this debilitating condition. The screening protocol should look at using an algorithm based on quantifiable clinical measures (i.e. quantitative sensory testing) rather than just risk factors.

The ideal screening protocol will enable clinicians to predict the likelihood of patients developing persistent pain post-TKR and:

- (i) Use suitable interventions to resolve the pre-existing pain conditions before TKR, hence reducing the likelihood of developing persistent pain post-TKR; or
- (ii) Try a different approach to conservative management in lieu of TKR surgery.

Competing Interests: No relevant disclosures.

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Chapter 2: Management of Pain Disorders

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2.1 Introduction

This unit presents current pain knowledge and skills that will be applicable to students in the area of musculoskeletal physiotherapy and related interdisciplinary areas. This unit aligns with the International Association with the Study of Pain Curriculum on Pain for Physical Therapists (2012): <http://www.iasppain.org/Content/NavigationMenu/GeneralResourceLinks/Curricula/Therapy/default.htm>.

The unit takes a patient-centered interdisciplinary approach to translate pain science knowledge into clinical practice and better integrate low technology approaches (empathy, narrative) with clinical evidence and current neurobiology. The aim is to help clinicians deliver 'the right care to the right patient at the right time with the right team', 'to improve quality of life for people with pain and their families, and to minimise the burden of pain on individuals and the community'.

This unit will address the key clinical roles and responsibilities a physiotherapist is likely to undertake in working with pain patients.

These include:

1. Assessment of pathophysiological processes (infection/inflammation), biomechanical factors (stress/strain), motor control strategies (adaptive and maladaptive) and cognitive and behavioural factors that contribute to a patient's pain, physical dysfunction and disability.
2. In collaboration with the patient, development of a management program directed at modifying the effect of physical and behavioural contributors to a patient's pain and disability and reduction of the factors that may lead to the recurrence of pain and disability.
Interventions discussed will focus on appropriate patient education, the appropriate use of paced exercise and activity, appropriate use of manual therapy and the importance of engaging empathetically with the patient to facilitate early, focused and appropriate sensory-motor strategies as appropriate to their pain disorder.
3. Liaison and referral within an interdisciplinary team approach.

Physiotherapists need to recognise when additional or alternate interdisciplinary help is required in order to assist the patient in pain. Psychological and behavioural factors can impact significantly on a patient's pain experience and disability and may predict chronicity. Pain responses which impact on a patient's behaviour, symptom management and mood will be discussed and issues which indicate referral to a behavioural medicine psychologist highlighted. Sufficient knowledge about pharmacological agents and their side effects will be presented as a means to support proper usage of medication by clients/patients and to optimise the 'therapeutic window' offered to encourage the use of active physical and behavioural management as appropriate for each individual patient. The contact time for this unit was 36 hours.

2.2 Syllabus

- An interdisciplinary approach to the management of pain disorders aimed at encouraging professional collaboration.
- The focus of the unit is the pain experience of patients and the physiological, psychosocial, and environmental components of that experience, with an application of profession-specific theoretical frameworks to assess and manage pain and disability.

2.3 Learning Outcomes

1. Recognise and analyse pain mechanisms and apply current theories on related clinical manifestations of pain relevant to highly skilled practice.
2. Evaluate the social, cultural and environmental implications associated with the experience, assessment and management, of musculoskeletal pain.
3. Differentiate between acute and chronic musculoskeletal pain and evaluate the implications for assessment and management of people in pain.
4. Critically appraise assessment and intervention strategies and outcome measures for pain management.

5. Formulate collaborative interdisciplinary intervention strategies consistent with a high level of practice.

2.4 Assessments

The work handed in for assessment in this unit were:

2.4.1 Written Exam

- This assessment comprised of short answer questions based on the first 4 weeks of lecture materials.

2.4.2 Clinical Case Study

- This assignment required presentation of one of my patients with persistent complex, musculoskeletal pain as a case study. This should not be a person with low back pain as this has been covered extensively in class.
- The aim of the assignment is to demonstrate my ability to integrate basic and clinical pain science into a framework that can be used to help better manage patients with musculoskeletal pain.

2.4.3 Medical Communication

- The aim of this assessment is to demonstrate integration of the basic and clinical pain science into a framework that can be used to help better communicate with doctors and other health professionals involved with the clinical management of people with musculoskeletal pain. This assessment links with and extends the clinical case study presented above.

2.4.1 Written Exam

Question 1

Using your knowledge and understanding of the differences between human nociception and pain:

- (i) **Briefly and clearly** expand on this difference with reference to acute and chronic musculoskeletal pain.
- (ii) What are the **implications** of this difference in term of clinical management?

Answer

- (i) Nociception is an input into the system, and pain is an output (final expression of all the filtering and processing). Nociception is the specialized apparatus that takes the stimulus that's of sufficient magnitude or duration to excite the nociceptive apparatus. Whether or not that's expressed as pain is what the brain decides to do with it. Pain is the final product of activity in distributed networks (interaction of multiple cortical and subcortical areas). Perception of pain depends on the nature of the pain and the context of each individual's experience. Actual tissue damage is not needed to experience pain.
Acute pain implies actual (or potential) tissue damage/injury with duration of less than 3 months. If there is an injury or insult, and if the noxious stimulus is of significant magnitude or duration, there is an activation of nociceptors. The impulse is then transmitted to the 1st order neurons along the primary afferents into the spinal cord and up to the 2nd and 3rd order neurons. Whether this input results in an expression of pain depends on the brain.
Chronic pain is due to the neuroplastic changes in the central nervous system with duration of more than 3 months. It may be from nociceptive pain initially that transition into chronic pain. However, chronic pain does not always need acute pain as a precedent.
- (ii) Pain is individual and as clinicians it is important that we see the whole person (as it affects the biology of the whole person). An individual's expression of pain is tied to the context of their sensory and emotional experience. We have to understand the type of questions that we need

to ask the patients, as purely asking about the nature of pain can be meaningless as opposed to finding out the context of their pain experience. Actual tissue damage is not needed for an expression of pain. It's the potential tissue damage that the brain decides on that might express pain, not just actual tissue injury.

Question 2

Current best practice pharmacologic management of acute musculoskeletal pain (nociceptive, inflammatory; non-cancer) recommends the use of non-opioid analgesia including paracetamol +/- NSAIDS (non-selective or coxibs).

- (i) Explain why you might combine these agents
- (ii) Indicate which NSAIDs would be **most appropriate** given the current evidence (risk/benefit for non-selective versus COX-2)
- (iii) Specify the proposed mechanism(s) of action for paracetamol and NSAIDS (non-selective and coxibs)

Answer

- (i) Combination of paracetamol with NSAIDs results in better analgesia with fewer side effects. The improved anti-nociception is due to synergistic/additive effects. Lower dose of each drug is needed; hence there is decreased severity of side effects from each drug.
- (ii) COX-2 selective NSAIDs are the most appropriate given the current evidence. COX-2 selective NSAIDs have been shown to have:
 - a. Rate of ulcers comparable to placebo
 - b. Less blood loss as compared to Non-selective NSAIDs
 - c. Less (negative) effect on bone healing as compared to Non-selective NSAIDs

COX-2 selective NSAIDs are advantageous (as compared to Non-selective NSAIDs) in:

- a. Patients at increased risk of GI ulcers

- b. Patients with a past history of aspirin-induced asthma

In randomized control trials, there have been no differences between Non-selective NSAIDs and COX-2 selective NSAIDs in renal and cardiovascular adverse events. However, epidemiological studies have shown the COX-2 selective NSAIDs are better for the kidney and celecoxib is better for the heart.

(iii) The mechanism of action for paracetamol is unclear. The current proposed mechanisms of action for paracetamol are:

- a. Interaction with radical prostanoid intermediate
- b. Inhibition of COX-3 in the brain, without COX-1 or 2 effects
- c. Interaction with serotonin pathway
- d. Interaction with NMDA receptor/NO synthetase

NSAIDs (non-selective and coxibs) work by inhibiting cyclo-oxygenase, which convert arachidonic acid to prostaglandins. Non-selective NSAIDs block both COX-1 and COX-2. Whereas coxibs work by only inhibiting COX-2.

Question 3

Manipulation-induced analgesia associated with manual therapy treatments (i.e. mobilisation/manipulation) is proposed to involve various interacting biological mechanisms

(i) Describe the mechanisms, pathways and neurotransmitters proposed to be associated with manipulation-induced analgesia

(ii) Describe what the specific therapeutic effect(s) might be

Answer

(i) The basic model of the mechanisms of manipulation-induced analgesia (MIA) is multifactorial and encompasses segmental inhibition, psychological effects, joint repair, influence of the chemical environment in the joint that reduces nociceptive input and descending inhibition. Most of the research has focused on the pain response immediately after treatment, and whether that is predominantly due to

segmental inhibition or descending inhibition. Further research has shown that descending inhibition is the most likely mechanism of MIA. Descending systems project down from the brain into the spinal cord and starts in areas like the frontal cortex, amygdala and hypothalamus. This then projects down into the periaqueductal grey and down into various nuclei in the medulla (i.e. nucleus raphe magnus) that then send neurons down to the spinal cord, and those neurons can then act to modulate pain by (1) kick-starting the inhibitory interneurons, (2) presynaptic inhibition, or by (3) directly inhibiting the pain projection neurons.

The study by Skyba et al. (2003) shows that the key neurotransmitters associated with MIA are serotonin (5-HT) and noradrenaline (NA). The activation of 5-HT and NA descending neurons coming down from the brain and down to the spinal cord, synapses (5-HT_{1A} and α_{2A} receptors) with pain projection neurons in the dorsal horn (that are going up to part of spinothalamic tract and spinomesencephalic tract) and is having a direct inhibitory effect on those neurons.

(ii) The specific therapeutic effects of manipulation-induced analgesia are:

- a. Rapid onset analgesia that happens within seconds to minutes after treatment
- b. Modality specific effect (no influence on thermal pain) mainly to mechanical pain
- c. Cumulative analgesic effect (stepwise improvement with fairly closely spaced treatment sessions)
- d. Crudely somatotopically organized analgesic effect
- e. Relationship between hypoalgesia and sympathoexcitation
- f. Non-opioid (serotonin mediated) analgesia

Question 4

Mechanical hyperalgesia and allodynia are clinical correlates commonly associated with acute and chronic musculoskeletal pain. These clinical correlates are proposed to reflect peripheral and central sensitisation processes.

(i) Explain the neuronal and non-neuronal mechanisms proposed to underlie these clinical correlates as they relate to acute and chronic musculoskeletal pain

Answer

(i) Peripheral sensitization is a physiological event where there is increased responsiveness and reduced threshold of nociceptors to stimulation of their receptive fields. The clinical correlates of peripheral sensitization are localised pain and sensitivity, spontaneous pain, hypersensitivity, allodynia and hyperalgesia. In acute musculoskeletal pain, injury and inflammation of the damaged tissues leads to profound changes in chemical milieu of nociceptors. Which leads to a decrease in nociceptors threshold and increased responsiveness to subsequent stimuli. Phosphorylation dramatically alters activity of receptors and ion channels. In summary, the physiologic principles of peripheral sensitization are changes in nociceptor properties, altered receptor-ion channels, increased membrane excitability, activation signalling cascades (phosphorylation proteins; gene transcription) and phenotypic switch (where the way the nerve fibres (C, A β , A δ) function changes as it relates to light touch driving sensitivity).

Central sensitization is a physiological event where there is increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold input. This phenomenon is activity-independent (does not require ongoing nociceptive input). The clinical correlates of central sensitization are widespread pain, spontaneous pain, hypersensitivity, allodynia, primary and secondary hyperalgesia, visceral sensitivity and referred pain. The physiologic principles of central sensitization are similar to that of peripheral sensitization. The main difference is that the processes occur in the central nociceptors transmission neurons in the dorsal horn or in the spinal nucleus of the trigeminal. There is also phenotypic switch of nociceptor specific neurons to WDR. The 3 key phases which increases sensitivity of the central nervous system are phosphorylation, trafficking and transcription.

An example is an acutely sprained ankle where there is initially a stimulus-response couple (putting weight on the ankle is painful, taking weight off reduces/stops the pain), and an area of hyperalgesia where the damaged tissues are. If this pain becomes chronic and we know that the damaged tissues have healed, but the patient has no stimulus-response coupling (ankle is painful regardless of whether weight is put on it), and widespread hyperalgesia (not just at site of previous injury at the ankle).

Question 5

You are considered an expert in musculoskeletal pain. You are **interviewed on national radio** about “nerve-related” pain. The phone lines are opened for callers: Roger, a 34 years old male building labourer, phones in to the radio station. He thinks he might have “nerve” pain (i.e. neuropathic pain) in his right leg.

Using **simple, non-jargonistic language, that is appropriate for a radio audience and is neurobiologically plausible (i.e.; accurate), address Roger’s query by:**

- (i) Indicating what specific questions you would ask to help sort out if he has neuropathic pain. Note: also indicate the answers that would suggest neuropathic pain

- (ii) Indicating to him what pharmacologic options might be appropriate to discuss with his doctor given he is also anxious and that NSAIDS have not helped

Answer

- (i) Hi Roger, thank you for calling. In order for me to help you, I would need to ask you a few questions. The questions are:
 - a. Question: Can you describe the pain that you are experiencing?
Burning, shooting, electrical shocks and/or stabbing sensations add credence to the theory that he might be experiencing

neuropathic pain.

- b. Question: Do you experience any tingling, pins and needles, numbness or ants crawling sensation in or near your area of pain?

Presence of the above sensations might suggest neuropathic pain.

- c. Question: Does the presence of clothes or a blanket that is in contact with the affected area cause you pain?

A positive response indicates that he is suffering from allodynia, which suggests the presence of neuropathic pain.

- d. Question: Is the affected area painful if you have a hot or cold shower?

A positive response indicates that he is suffering from thermal hyperalgesia, which suggests presence of neuropathic pain.

- e. Question: If you apply light pressure to the area of pain, does your pain get worse?

A positive response indicates that he is suffering from mechanical hyperalgesia, which suggests presence of neuropathic pain.

- (ii) In your case, I would advise discussing with your doctor about the use of pregabalin for your pain. The other benefits of taking pregabalin are that it has been shown to reduce pain-related sleep interference and also helps with reducing anxiety. Combination therapy (combination of 2 or more drugs) is often helpful in managing nerve pain. Medicines like tramadol, tapentadol and/or topical lidocaine patches can be used in combination with pregabalin to optimise your pain relief. As I do not have your complete medical history, the medications that I am suggesting may or may not be suitable for your condition. I strongly recommend having a proper discussion with your doctor about this issue.

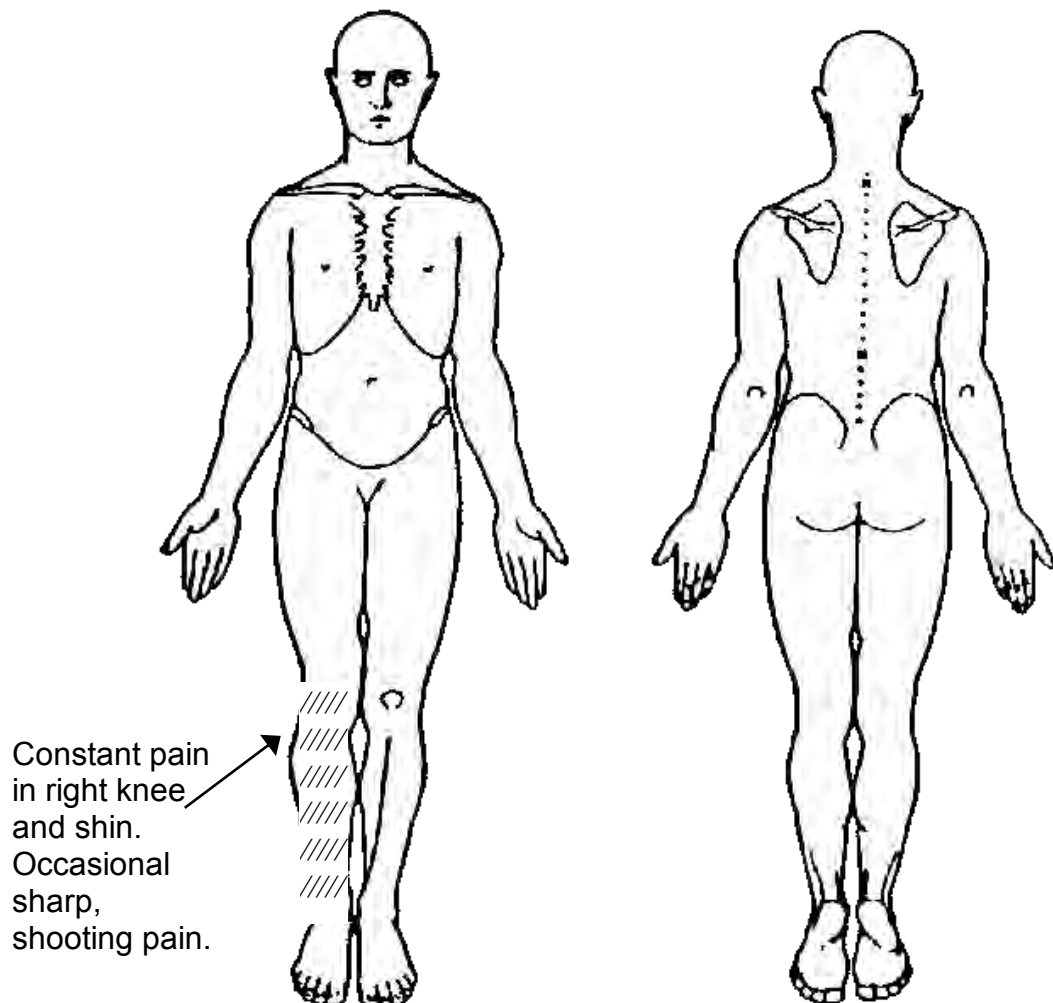
2.4.2 Clinical Case Study

1. Clinical Summary

Current History:

S.J. presented to the clinic in a wheelchair, and was accompanied by his wife. He is a 68 year-old cattle station owner who was diagnosed as having severe osteoarthritis (OA) of both knees in 2006. He states that he was coping well with his condition until 3 years ago, when he started to feel that the pain in his right knee started to worsen. He states that his pain has started to worsen even more over the last 6 months. He complains of pain from his right knee going down to his right shin (refer to body chart). S.J. states that he can walk a short distance (approximately 10 minutes) but he prefers not to use his knees too much as he does not want to “wear them out further”. He has a BMI of 30. S.J. was screened and cleared of any red flags.

Body Chart:



Pain History:

S.J. reports that he is in constant pain. 3 years ago before the pain worsened, he stated that his pain was 5/10 on average then. Since 6 months ago, his pain is 7/10 on average (With pain medication. Pain is 10/10 unmedicated). He states that pain shoots down from the right knee to the right shin, and he often feels a strange sensation (sometimes numbness, other times it feels like someone is sticking pins in) in that same area. His pain worsens when he has a cold shower. He is unable to wear jeans as the weight of the jeans resting/rubbing on his right knee and shin gives him pain. He is unable to do the physical work at the cattle station due to his pain. His functional limitations are squatting (unable to do at all), climbing up and down stairs (able to go up 2-3 steps but has to stop and rest for a couple of minutes due to pain), walking for 10 minutes and mustering cattle. S. J. reports that he is often unable to sleep for more than 2 hours at a time due to the pain in his right knee. He also has complains of morning stiffness in both his knees lasting about 15-20 minutes.

Social History:

S.J. does not smoke or drink, and has no other medical conditions. He lives on the cattle station, which is about a 4 hour drive from the nearest town (Newman, Western Australia), with his wife and 2 sons (35 and 38 years old). His youngest son had a spinal cord injury 3 years ago when he fell off his horse and is a paraplegic. As he is unable to do anything physical, his eldest son has taken over all of the physical tasks involved in the running of the cattle station. He has put on about 20-25 kg over the last 3 years. He states that this is due to the lack of physical activity (because of fear of further damage to his knees) and also his eating habits (frequent snacking of sweets and having big meals everyday). His wife was diagnosed with breast cancer 4 years ago, she received treatment and the cancer went into remission. However, during a follow up screening 6 months ago, the oncologist discovered that the cancer has relapsed and has spread into her lymph nodes. He accompanies his wife to Perth for her treatment fortnightly.

Medication:

S. J. is currently on Etoricoxib (60mg, once daily) and Tramadol ER (100mg, thrice daily). He has been on these medications and dosage for the last 2 years.

Investigations:

Radiographs of both knees show severe joint space narrowing and presence of multiple osteophytes.

Screening Tools and Outcome Measures:

The Patient-Specific Functional Scale (PSFS), PainDETECT, Pain Catastrophizing Scale (PCS), Tampa Scale for Kinesiophobia (TSK) and DASS 21 questionnaires were administered.

Based on the PSFS, S. J. listed the following 4 activities:

- Mustering cattle – 0/10 (Unable to perform activity)
- Walking for 10 minutes – 2/10 (Severe impairment in performing activity)
- Walking up and down stairs – 2/10 (Severe impairment in performing activity)
- Squatting – 0/10 (Unable to perform activity)

S.J. scored 30/38 for the PainDETECT questionnaire. Due to the high score on the PainDETECT, it is likely that a neuropathic pain component is present. A score of >19 indicates that a neuropathic pain component is likely.

He scored 45/52 for the PCS (Rumination: 15, Magnification: 10, Helplessness: 27); this indicates that he demonstrates catastrophic thinking, which plays a role in heightening his pain intensity and magnification of his pain. A score of 30 represents a clinically relevant level of catastrophizing.

S.J. scored 65/68 for the TSK; this means that he has a high degree of kinesiophobia (irrational fear of movement due to vulnerability of re/injury). A score of 37 differentiates between high and low scores of kinesiophobia. For the DASS 21 questionnaire, his scores were: 21 (Depression Score); 6 (Anxiety Score); 20 (Stress Score). Based on the DASS 21 scores, S. J.

has extremely severe depression scores, moderate anxiety scores and extremely severe stress scores.

Pain Management:

Due to the remote location of the cattle station, S. J. has limited access to health care. He is currently only under the care of the general practitioner (GP) in Newman, which he sees infrequently.

Patient Perspective:

S.J. expressed anger, anxiety and feeling very stressed over several issues (e.g. future of the cattle station, difficulty with caring for his paraplegic son, wife's cancer relapse). He would like to be able to get back to doing some physical work around the cattle station, however he tries not to move around much as he is worried about causing more damage to his knees. His GP has mentioned that a total knee replacement (TKR) might be a good solution for his knee pain, but S.J. is not keen as he has a few friends that have had bad experiences after having had a TKR (worse pain after TKR, infection and no change in pain). He states that the only activity that he finds enjoyable now is eating. He feels like there is no joy in life anymore, and the thought of losing his wife is too much to bear. S.J. also mentioned that he has 2 shotguns at home and he has thought that there is no point in living at times.

Physical Examination Findings:

- Knee Flexion:
 - Right: 90 degrees, P1 R2, 8/10 pain. 120 degrees, P2, 10/10 pain.
 - Left: 120 degrees, P1 R2, 6/10 pain.
- Functional:
 - Squat: ¼ squat, 9/10 pain. ½ squat, 10/10 pain. Unable to squat fully.
 - Stairs: Up – Leads with left leg, and moves up step one at a time. Able to go up a maximum of 3 steps before needing to rest due to 10/10 pain. Down – Leads with right leg, and

moves down step one at a time. Able to go down a maximum of 3 steps before needing to rest due to 10/10 pain.

- Sit to stand = Uses arms to push up when standing. No eccentric control of knees when sitting down. Drops straight into chair when sitting.
- Sensory testing:
 - Light touch with brush = 10/10 pain reproduced at right knee and shin.
 - Light pressure = 10/10 pain reproduced at multiple sites (bilateral thighs, knees, shins and elbows).
 - Cold (using test tube filled with ice water) = 10/10 pain reproduced at right knee, shin and elbow.

Summary:

It is clearly evident that S. J. has both nociceptive and neuropathic pain, as well as features of peripheral and central sensitization. This is compounded by psychological factors (kinesiophobia, catastrophic thinking, and high DASS 21 scores - extremely severe depression scores, moderate anxiety scores and extremely severe stress scores) and his passive pain coping mechanisms. It is important to note that the timing of his worsening pain coincides with major negative events that have happened to his family.

2. Case Interpretation

OA Background

OA pain is complex; nociceptive, neuroplastic and neuropathic pain mechanisms, in combination with psychological and social factors (e.g. pain catastrophising, depression, anxiety, lack of social support, lower socioeconomic status) have been shown to contribute to the generation of OA pain⁽¹⁾. The presentation of pain in knee osteoarthritis sufferers varies greatly, from localised activity-related pain to referred or even widespread pain at sites distant from the knee⁽¹⁻⁴⁾.

There are multiple mechanisms (nociceptive pain, neuroplastic pain and neuropathic pain), pain processes (peripheral sensitization, central sensitization), and psychological/social factors that contribute to the generation of OA pain^(1, 5). To further complicate the nature of OA pain; the mechanisms, pain processes and factors that mediate OA pain vary among individuals^(1, 5).

Management of knee OA is generally based on symptom severity and range from:

- (iv) Non-pharmacological interventions (e.g. Weight reduction, Lifestyle modification, Exercise rehabilitation)
- (v) Pharmacological interventions (e.g. NSAIDS, Analgesics)
- (vi) Surgical interventions (e.g. Arthroscopy, Total knee replacement) when both non-pharmacological and pharmacological interventions have failed

Current Neurobiology Pain Perspective:

Based on the clinical findings, S.J.'s pain profile comprises of nociceptive, inflammatory and neuropathic pain

The evidence that supports the presence of nociceptive pain are:

- Knee range-of-motion
- Functional tasks (limitations)

The evidence that supports the presence of inflammatory pain are:

- Morning stiffness in knees
- Allodynia in affected area (as evidenced by light touch with brush)

- Mechanical hyperalgesia in affected area (as evidenced by light pressure)

The evidence that supports the presence of neuropathic pain are:

- High PainDETECT questionnaire score (30/38)
- Shooting pain from right knee to shin
- Pins and needles and numbness in the affected area
- Pain in the affected area if he has a cold shower
- Weight of jeans on his right knee and shin gives him pain
- Cold hyperalgesia in affected area
- Allodynia in affected area
- Mechanical hyperalgesia in affected area

S.J. also appears to have features of peripheral sensitization (localised pain and sensitivity) and central sensitization (widespread sensitivity to light pressure and cold). Injury and inflammation results in profound changes in the chemical milieu of the nociceptors. This leads to increased responsiveness and reduced threshold of nociceptors to stimulation of their receptive fields. Post-translational processing (phosphorylation) and altered gene expression are the main mechanisms of peripheral sensitisation⁽⁶⁾. Spontaneous ectopic activity and the constant barrage of nociceptive input from the osteoarthritic knee most likely initiated the central sensitization^(6, 7).

His pain is also compounded by the presence of psychological distress (i.e. depression, anxiety, stress) and his belief systems (i.e. passive pain management mentality, kinesiphobia, pain catastrophising). Stress causes the hypothalamus to secrete CRH, which stimulates the pituitary to secrete ACTH, which then stimulates the synthesis of cortisol.

Simultaneously, the adrenal glands are stimulated and secrete adrenalin. Uncontrolled stress leads to the impaired regulation of the immune and stress systems which have been found to have links between mood disorders and inflammatory disease⁽⁸⁾. Catastrophising, anxiety, fear of movement and individual's experiences and belief systems can act to increase the perception of OA pain⁽⁹⁾.

Current Clinical Guidelines:

Based on the current guidelines for conservative management of patients with knee OA⁽¹⁰⁾, there are a number of gaps in the management of S.J.'s condition. The gaps that need to be addressed are:

1. Education of his condition
 - a. S.J. was never educated on his condition and has no clear understanding of the pathophysiology of OA and the current clinical best practice guidelines on the treatment of OA.
 - b. There is a pressing need to change his current belief system on the management of his condition, this will help to change his passive approach to pain management to a more active one.
2. Prescription of an appropriate exercise program
 - a. The success of an appropriate exercise program for him will depend on his understanding of his condition, as well as changing his belief system to be in line with an active pain management approach.
 - b. Low impact exercises and strength training will make up the basis of his exercise program.
3. Weight management plan
 - a. S.J.'s BMI is 30, which puts him in the obese range. As per current best practice guidelines⁽¹⁰⁾, reduction in weight has been shown to reduce pain levels.
4. Pharmacological management plan
 - a. He is currently on the maximum dosage of Etoricoxib and Tramadol ER. But his pain levels are still not well controlled. Current guidelines⁽¹⁰⁾ recommend the use of NSAIDs as being appropriate for chronic knee OA pain, however, the efficacy of opioids are uncertain. Duloxetine has been flagged as being appropriate for use in chronic knee OA pain, and hence might be suitable for use in S.J.'s case. However, it is important to note that based on his DASS 21 scores, there is a strong likelihood that S.J. might be

diagnosed as having depression. Pharmacological treatment for depression includes use of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSNRIs). Hence it is important that he is not prescribed high dose TCAs or SSNRIs if he is on duloxetine for the knee pain, as that could lead to serotonin syndrome. Use of tramadol is not suitable for S.J., as there is a precaution for use of tramadol on individuals that have a suicide risk. Furthermore, if he is diagnosed as being clinically depressed, tramadol has a precaution for use for individuals that are on TCAs and SSNRIs.

- b. As S.J.'s pain has a neuropathic component, it is important that he is treated pharmacologically for it. Current evidence⁽⁷⁾ recommends treating neuropathic pain with low dose TCAs, SSNRIs, calcium channel α_2 - δ ligands, topical lidocaine or opioid agonists. Opioid agonists like tramadol may not be suitable for S.J. due to his suicide ideation, and if he is prescribed any type of SSNRIs (e.g. duloxetine). The use of TCAs and SSNRIs for the treatment of his neuropathic pain might not be suitable, pending his diagnosis of depression and pharmacological treatment. The most logical pharmacological treatment for S.J.'s neuropathic pain is a combination of pregabalin and lidocaine patch. A benefit of pregabalin is the improvement of sleep disturbances and reduction in anxiety (which are 2 issues that S.J. has highlighted).

Gaps In Clinical Practice:

The current guidelines for conservative management of patients with knee OA are focused on treatment of nociceptive pain. However, 2 recent studies have found that close to 20% of knee OA sufferers reported components of neuropathic pain, using the PainDETECT questionnaire^(11, 12). The issue of neuropathic pain in knee OA sufferers is something that needs to be addressed.

Interdisciplinary Approach:

The utmost priority for S.J. is an urgent referral for him to be assessed by a mental health practitioner (e.g. psychiatrist, psychologist) due to his suicide ideation/risk. Due to the complexity of this case, a referral to a tertiary multi-disciplinary pain management clinic will be ideal.

S.J. will need to be reviewed by:

- Psychiatrist
 - To assess his psychological distress and suicide ideation
- Pain management doctor
 - To review, recommend and titrate medications that will suit his condition.
- Clinical/Behavioral psychologist
 - To change current belief system
 - Teach coping strategies
 - Help organize a better sleep pattern
- Physiotherapist (who specializes in managing chronic pain)
 - Educate S.J. on his condition
 - Change current belief system
 - Exercise prescription
 - Weight management
- Dietitian
 - Review and set a nutrition plan for weight control

3. Patient Management Plan

Refer to Appendix 1.

Please note that mustering of cattle is not in the current goals as it is complex activity that will require intensive rehabilitation (looking at a time frame of 3 to 6 months) before the possibility of it happening.

4. Summary (For Patient)

Refer to Appendix 2.

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Appendix 1

Patient Management Plan

Management Options	Details	Goals	Screening Tools/Outcome Measures
Education/Advice -Good quality of evidence for education and self management ⁽¹⁰⁾	-Educated S.J. on his condition. -Explained that pain does not necessarily mean damage/harm. -Explained that normal movement will not damage his knees further and will in fact help with the pain. -Education on the effects of stress and belief systems on perceived pain. -Gave S.J. some resources (Explain Pain book and painHEALTH website) for him to have a look at.	<u>STG</u> : Changing his current belief systems and increasing knowledge of pain. Encourage movement and positive thinking. <u>MTG/LTG</u> : Reduction of TSK to <37, PCS to <30 and global reduction of DASS 21 scores.	Tampa Scale for Kinesiophobia Pain Catastrophizing Scale DASS 21

<p>Exercise Plan</p> <p>-Good quality of evidence for incorporation of strength/exercise program⁽¹⁰⁾</p>	<p>-Reinforced that movement is not harmful and that an increase in physical activity will help with his condition.</p> <p>-Walking – start with short distances (8 minutes) but do so frequently (3 times) throughout the day.</p> <p>-Home exercises – Straight leg raise in supine (3 sets of 5 repetitions with 5 seconds hold), Bridging (3 sets of 5 repetitions with 5 seconds hold), Knee extension in supine with rolled up towel under knee (3 sets of 5 repetitions with 5 seconds hold), Wall squats (3 sets of 5 with 5 seconds hold).</p>	<p><u>STG</u>: Walking – 3 x10 mins daily</p> <p>Home Ex – 3 sets of 8 repetitions with 5 secs hold</p> <p><u>MTG</u>: Walking – 2 x15 mins daily</p> <p>Home Ex – 3 sets of 8 repetitions with 8 secs hold</p> <p><u>LTG</u>: Walking – 30 mins daily</p> <p>Home Ex – 3 sets of 10 repetitions with 10 secs hold</p>	<p>Patient-Specific Functional Scale</p> <p><u>STG</u>: Walking for 10 mins, 4/10</p> <p>Stairs (Up/Down – 5 steps), 4/10</p> <p>¼ squat, 2/10</p> <p><u>MTG</u>: Walking for 15 mins, 5/10</p> <p>Stairs (Up/Down – 8 steps), 5/10</p> <p>½ squat, 3/10</p> <p><u>LTG</u>: Walking for 30 mins, 7/10</p> <p>Stairs (Up/Down – 10 steps), 7/10</p> <p>½ squat, 5/10</p>
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Weight Management -Good quality of evidence for weight management ⁽¹⁰⁾	<ul style="list-style-type: none"> -Look at current diet, and reduce portion size. -Reduce consumption of soft drinks and sweets. -Increase daily activity 	<p><u>STG:</u> Reduce soft drink and sweets intake by 50%. Drop 4 kgs</p> <p><u>MTG:</u> Drop 8 kgs</p> <p><u>LTG:</u> Drop 12 kgs</p>	
Return To Work	<ul style="list-style-type: none"> -To start with light physical work such as walking for short distances along the boundary of the cattle station to check for damaged fences and pumps for the watering holes -Mustering cattle on horseback is an activity that will be looked at in future 	<p><u>STG:</u> <u>Driving out to check on fences and watering holes and walking for short distances (5 mins)</u></p> <p><u>MTG:</u> Climbing up a flight of steps to check on water tanks</p> <p><u>LTG:</u> ½ squat to check on power generator</p>	Patient-Specific Functional Scale

Medication -Good quality of evidence for use of COX-2 inhibitors ⁽¹⁰⁾ -Lidocaine patch and pregabalin is recommended for use as a first-line treatment for neuropathic pain ⁽⁷⁾	-Continue with Etoricoxib, advised that tramadol might not be suitable for him. -To explore use of pregabalin and lidocaine patch with GP/Pain Management doctor.	<u>STG</u> : Review of medication with GP/Pain Specialist <u>MTG/LTG</u> : Effective use of medication	PainDETECT <u>STG/MTG/LTG</u> : Reduction of PainDETECT scores to indicate control of neuropathic pain component
Referral To Others	-Spoke at length about the findings of DASS 21 questionnaire. Arranged for S.J. to see a GP in Perth on the same day. -GP to do an assessment of his mental state and arrange for referral to see psychiatrist. -Arranged an appointment for S.J. to be seen at a pain management clinic, where a pain management doctor and	<u>STG</u> : Review by GP on same day to assess mental state and arrange referral to psychiatrist. Assessment by pain management clinic and dietitian	Tampa Scale for Kinesiophobia Pain Catastrophizing Scale DASS 21 -Reduction in the scores of the above instruments

	<p>clinical/behavioral psychologist will see him.</p> <p>-Arranged an appointment for him to be seen by a dietitian.</p>	<p><u>MTG/LTG</u>: Review with the pain management clinic and dietitian as needed</p>	
Review	<p>In 2 weeks when he returns for his dietitian and pain management appointment</p> <p>Subsequent appointments will be every fortnight (tagged to wife's appointments in Perth), and as required.</p>		

Appendix 2

Summary (For Patient)

Management Options	Comments
Education/Advice	Explanation about knee OA and how normal movement will help your condition. Pain does not necessarily mean damage/harm. Stress and your current beliefs about pain are aggravating your condition. I am going to loan you a book titled "Explain Pain" which will give you more insight into your pain. You can also have a look at this website (http://painhealth.csse.uwa.edu.au/pain-management-making-sense-of-pain.html). Stay positive and find ways to incorporate more movement into your daily routine. Goal: Start to be more physically active as that can help with your stress levels. Keep a positive outlook.
Exercise Plan	Your path to recovery begins with being regular with your exercise and physical activity. Goal: Start with walking short distances (8 minutes) but do so frequently (3 times) daily. Home exercises – Straight leg raise in lying, Bridging, Wall squats (3 sets of 5 repetitions with 5 seconds hold), Knee extension in lying with rolled up towel under knee (3 sets of 5 repetitions with yellow theraband). I will progress your exercises as we go along.
Weight Management	Based on your BMI, you are in the obese range. Reduction of weight has been shown to be beneficial to reducing your pain levels. Goal: Reduce portion size. Reduce consumption of soft drinks and sweets by 50%. Increase daily activity. Aim to lose a 1 kg of weight per week.

Medication	<p>There is a need to review your pain medication. You should continue with Etoricoxib, however tramadol might not be suitable for you. As your pain has a neuropathic component, there is a need to explore use of pregabalin and lidocaine patch with the GP/Pain Management doctor. Goal: The right medication will play a role in controlling your pain levels. The pain specialist will come up with a medication plan for you. This will typically involve quick acting and sustained pain-relieving medication. It is important that you know what medication is for which type of pain. Once you have worked out a “rescue plan”, remember to share this with your family and let them know what it is.</p>
Referral to others	<p>See the GP next door for an assessment on your mental health and also to discuss medications. The GP will arrange for referral to see psychiatrist if needed. I have arranged an appointment at the pain management clinic, where a pain management doctor and clinical/behavioral psychologist will assess you. The psychologist can help you with coping strategies and managing your mood. I have also arranged an appointment for you to see a dietitian who will work out a nutrition plan for you.</p>
Review	<p>I will see you in 2 weeks when you come back to Perth for your dietitian and pain management appointments. During that appointment I will review your progress and go through the mid term goals and long term goals again. I will give you a phone call in a week's time to see how you are faring.</p>

2.4.3 Medical Communication

Dr Glenn Liew
St Francis Medical
11/29 Station Street
Subiaco, WA 6008

29th September 2014

RE: Mr S.J. (DOB: 01/01/1946)

Dear Glenn,

Thank you for agreeing to review S.J. at such short notice.

Presenting disorder: S.J. is a 68-year-old male, who presented to the clinic today due to right knee pain. He was diagnosed with severe osteoarthritis (OA) of both knees in 2006. He states that he was coping well with his condition until 3 years ago, when he started to feel that the his right knee pain worsened. His pain has increased even more over the last 6 months

Brief subjective pain history and behavior: S.J. reports that he is in constant pain. 3 years ago before the pain worsened, he stated that his pain was 5/10 on average then. Since 6 months ago, his pain is 7/10 on average (with pain medication. Pain is 10/10 un-medicated). He states that pain shoots down from the right knee to the right shin, and he often feels numbness/pins and needles in that same area. His pain worsens when he has a cold shower. He is unable to wear jeans as the weight of the jeans on his right knee/shin gives him pain. S.J. reports that he is often unable to sleep for more than 2 hours at a time due to pain. He also has complains of morning stiffness in both his knees lasting about 15-20 minutes.

Behavioral responses to pain: S.J. turned up for his appointment with me today in a wheelchair, as he prefers not to use his knees too much as he does not “wear them out further”. He has also stopped all physical work at the cattle station due to this belief.

Social history: S.J. does not smoke, drink or have any history of drug abuse. He lives on the cattle station (4 hours drive from Newman), with his wife and 2 sons (35 and 38 years old). His youngest son fell off his horse 3 years and is now a paraplegic. S.J.'s eldest son has taken over all of the physical tasks involved in the running of the cattle station. He has put on about 20-25 kg over the last 3 years (due to the lack of physical activity and eating habits). His wife recently (6 months ago) had a relapse of breast cancer. S.J. feels like there is no joy in life anymore, and the thought of losing his wife is too much to bear. He also mentioned that he has 2 shotguns at home and he has thought that there is no point in living at times.

Medical non-pain and pain co-morbidities: S.J. has no other medical conditions. He was screened and cleared of any red flags.

Screening Tools and Outcome Measures: S.J. scored 30/38 for the PainDETECT questionnaire. A score of >19 indicate that a neuropathic pain component is likely.

S.J. listed the following 4 activities on the Patient-Specific Functional Scale:

- Mustering cattle – Unable to perform activity
- Walking for 10 minutes – Severe impairment in performing activity
- Walking up and down stairs – Severe impairment in performing activity
- Squatting – Unable to perform activity

He scored 45/52 for the Pain Catastrophizing Scale; this indicates that he demonstrates catastrophic thinking, which plays a role in heightening his pain intensity and magnification of his pain.

S.J. scored 65/68 for the Tampa Scale for Kinesiophobia; this means that he has a high degree of kinesiophobia (irrational fear of movement due to vulnerability of re/injury).

For the DASS 21 questionnaire, his scores were: 21 (Depression Score); 6 (Anxiety Score); 20 (Stress Score); indicating that he has extremely severe depression scores, moderate anxiety scores and extremely severe stress scores.

Pain mechanisms: S.J. has nociceptive, inflammatory and neuropathic pain, as well as features of peripheral and central sensitization. This is compounded by psychological factors (kinesiophobia, catastrophic thinking, and extremely severe depression scores, moderate anxiety scores and extremely severe stress scores on the DASS 21) and his passive pain coping mechanisms. It is important to note that the timing of his worsening pain coincides with major negative events that have happened to his family.

Pain management strategies to date and outcome: Due to the remote location of the cattle station, S.J. has limited access to health care. He is currently only under the care of the general practitioner (GP) in Newman, which he sees infrequently. S.J. has been on Etoricoxib (60mg, once daily) and Tramadol ER (100mg, thrice daily) for the last 2 years.

Physical examination findings and interpretation:

- Knee flexion ranges were restricted and painful which are consistent with degenerative OA changes. Right knee flexion was more restricted and painful compared to the left.
- Functionally, S.J. was unable to do a full squat due to pain (able to do ½ squat with 10/10 pain); Up/Down stairs only a maximum of 3 steps at a time (due to pain); needed to use arms to push up with standing and was unable to control descent when sitting down.
- Generalised mechanical and cold sensitivity: sensitivity to light touch at right knee and shin; sensitivity to light pressure at bilateral thighs, knees, shins and elbows; sensitivity to cold at right knee, shin and elbow.

Management plan: Based on the current guidelines⁽¹⁾ for conservative management of patients with knee OA, please refer to Appendix 1 for the management plan for S.J.

Recommendations: Following my assessment of S.J., I make the following recommendations.

1. Review of mental state: Apart from the results of the DASS 21 questionnaire, I am also concerned that S.J. has showed signs of suicide ideation. Would you be able to do an assessment on his mental state and arrange any appropriate referrals?
2. Medications: S.J. will need to have his current pain medications reviewed. I would suggest continuing with Etoricoxib. However, tramadol might not be suitable for him. Kindly explore the use of pregabalin and lidocaine patch for his neuropathic pain.
3. Pain management: I have made arrangements for S.J. to be seen at PainCare in Fremantle on the 13th October 2014.
4. Nutrition: I have made arrangements for S.J. to be seen by a dietitian (Kate Fleming) on the 13th October 2014.
5. I will review S.J. after his pain management and dietitian appointments.

Regards,

Philip Cheong
APA Musculoskeletal Physiotherapist

References

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Chapter 3: Pharmacology for Health Professionals

3.1 Introduction

Pharmacology is the study of drugs, including their actions and effects in living systems. Knowledge acquired from this unit will provide health professionals with a sound understanding of pharmacological principles. As well as learning about the pharmacology of drugs acting on major body systems, including the cardiovascular, respiratory, endocrine and central nervous systems, health professionals will also learn about the mechanism of drug absorption, distribution, biotransformation and renal elimination. The contact time for this unit was 48 hours.

3.2 Syllabus

- Pharmacological principles.
- Mechanisms of drug absorption, distribution, metabolism and renal elimination.
- Half-life, clearance, drug concentration and effect.
- Relationship between rate of drug dosing and plasma concentrations.
- Bioavailability and bioequivalence.
- Renal disease and drug dosing - serum creatinine and creatinine clearance.
- Mechanisms of drug toxicity, adverse reactions, interactions.
- Meaning of information in drug monographs.
- Autonomic Nervous System pharmacology.
- Pharmacology of drugs acting on respiratory, gastrointestinal, cardiovascular, central nervous, endocrine and musculoskeletal systems.
- Drugs for pain, allergy and mental illness.
- Antimicrobial, antifungal and antiviral agents.

3.3 Learning Outcomes

1. Apply the pharmacological and pharmacokinetic principles of drugs affecting the major systems of the body.
2. Interpret and calculate the pharmacokinetic parameters of a drug and its use in designing drug dosage regimens.
3. Critically appraise literature relating to pharmacological and pharmacokinetic principles in the advancement in drug treatment/s.

3.4 Assessments

Assessment for this unit comprised of 3 online tests, a literature review essay and a final written examination. The completed examination scripts for the online tests and final written examination were not returned to students. Hence only the literature review essay is available:

3.4.1 Literature Review Essay

- For this assignment, I had to submit a literature review essay on a topic of my interest.
- The topic I had chosen was, “Examine the relevant literature and review advances in the understanding and management of neuropathic pain”.

3.4.1 Literature Review Essay

Title:

Examine the relevant literature and review advances in the understanding and management of neuropathic pain

Abstract:

Neuropathic pain arises as a direct consequence of a lesion or disease affecting the somatosensory system. This review focuses on the current understanding, clinical assessment and pharmacological management of neuropathic pain.

Introduction

In 1994, the International Association for the Study of Pain (IASP) defined neuropathic pain as, "Pain initiated or caused by a primary lesion or dysfunction in the nervous system."⁽¹⁾ This definition has been useful in differentiating neuropathic pain from other types of pain, but it is neither precise nor specific.

The IASP subsequently reviewed the definition of neuropathic pain in 2008 to be: "Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system."⁽²⁾ This revised definition of neuropathic pain emphasizes on the concept of aberrant somatosensory processing (far in excess of normal plasticity of the undamaged nociceptive system) which is the hallmark of neuropathic pain.

Neuropathic pain can be classified into either central (spinal, brainstem, thalamus or cortex) or peripheral (nerve, plexus, dorsal root ganglion or root), depending on the anatomic location of the lesion or disease.

Epidemiology

In France, neuropathic pain has been approximated to affect 6.9% of the French general population.⁽³⁾ In the United States of America, an estimated 35% of USA general population suffer from chronic pain, and 17.9% of those chronic pain sufferers have neuropathic pain.⁽⁴⁾

Due to the complex nature of neuropathic pain, it is often under diagnosed⁽⁵⁾ and not treated appropriately. To add to the complexity of neuropathic pain, sufferers of chronic/neuropathic pain also tend to have higher depression and anxiety scores and more sleep disturbances.^(6, 7)

Pathophysiology

Most of our understanding on the pathophysiology of neuropathic pain is based on animal studies.

The general mechanisms of neuropathic pain are peripheral and central sensitisation. The specific mechanisms are ectopic nerve activity, structural re-organization and loss of inhibitory interneurons

Following axonal injury (nerve lesion), a cascade of events takes place.

There is an upregulation in the $\alpha\delta$ Ca^{2+} subunits in the dorsal root ganglion neurons, which causes prolonged membrane depolarization of the calcium channels.⁽⁸⁾ A downregulation in μ opioid receptors has also been observed in animal studies of neuropathic pain states.^(9, 10) The nerve lesion causes upregulation of nerve growth factor (NGF), tumour necrosis factor α ($\text{TNF}\alpha$), transient receptor potential vanilloid type 1 (TRPV1) and pro-inflammatory cytokines.⁽¹¹⁻¹³⁾ The release of these products trigger the expression of sodium channels and sensitisation of the TRPV1 receptors in the nearby healthy nerve fibres.

Peripheral sensitisation sets in following a nerve lesion. Peripheral sensitization is a physiological event where there is increased responsiveness and reduced threshold of nociceptors to stimulation of their receptive fields. Injury and inflammation of the damaged tissues leads to profound changes in chemical milieu of nociceptors, which leads to a decrease in nociceptors threshold and increased responsiveness to subsequent stimuli. Phosphorylation dramatically alters activity of receptors and ion channels. Changes in nociceptor properties, altered receptor-ion channels, increased membrane excitability, activation signalling cascades (phosphorylation proteins; gene transcription) and phenotypic switch (where the way the nerve fibres (C, $\text{A}\beta$, $\text{A}\delta$) function

changes as it relates to light touch driving sensitivity) are the hallmarks of peripheral sensitization.⁽¹⁴⁾

Alterations in sodium channels (increased expression) and potassium channels (inhibition) occur following nerve lesion.⁽¹⁵⁻¹⁹⁾ This alteration in sodium and potassium channels, coupled with peripheral sensitization, causes ectopic nerve activity to occur.

The ectopic nerve activity is the primary driver of central sensitization in neuropathic pain. Central sensitization is a physiological event where there is increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub-threshold input.⁽²⁰⁾ This phenomenon is activity-independent (does not require ongoing nociceptive input). Phosphorylation of the NMDA and AMPA receptors dramatically increases their sensitivity. Phosphorylation of the NMDA receptor increases its distribution to the synaptic membrane and its responsiveness to glutamate, which causes increased excitability to the cell membrane.⁽¹⁴⁾ The physiologic principles of central sensitization are similar to that of peripheral sensitization. The main difference is that the processes occur in the central nociceptors transmission neurons in the dorsal horn or in the spinal nucleus of the trigeminal. There is also phenotypic switch of nociceptor specific neurons to wide dynamic range neurons. The low threshold A β and A δ fibres are then able to activate the second order nociceptive neurons in the dorsal root ganglion.

Selective loss of inhibitory GABAergic interneurons has been shown to occur in an animal model.⁽²¹⁾ Some animal studies have also shown a decrease in efficacy of descending inhibitory pathways and the endogenous endorphin system in neuropathic pain conditions.^(22, 23) The loss of inhibitory interneurons, decrease in efficacy of the descending inhibitory pathways and endogenous endorphin system, contributes to the complexity of managing neuropathic pain.

Clinical Assessment of Neuropathic Pain

Even though neuropathic pain is very heterogeneous, the clinical signs and symptoms are similar across the various neuropathic pain conditions/syndromes. Sufferers of neuropathic pain frequently exhibit paroxysmal, persistent and paradoxical pain that can be stimulus independent or stimulus evoked.

Sensory Testing

Neuropathic pain patients tend to present with both negative (Hypoesthesia, Pain-hypoesthesia, Hypoalgesia and Thermal hypoesthesia) and positive (Spontaneous: Paraesthesia, Superficial burning pain, Paroxysmal Pain; Evoked: Allodynia, Static hyperalgesia, Punctate hyperalgesia, Heat/Cold hyperalgesia, etc) sensory signs and symptoms.⁽²⁴⁾

The area of sensory abnormality must be compatible with the lesion site. Sensory testing (thermal-cold/heat, touch, vibration, pressure and pin prick) plays an important role in the clinical assessment. Sensory testing in the clinical environment can be assessed easily with common items. Thermal (cold/heat) testing can be accomplished by using a test tube filled with water at 20°C for cold testing, and water at 40-45°C for heat testing; touch can be assessed by response to gentle application of a piece of cotton wool; vibration by tuning fork placed at strategic bony landmarks; pressure by gentle pressure exerted by the healthcare practitioner's finger, and pin prick by response to a toothpick or sharp stimuli.⁽²⁴⁾

Screening Tools

Screening tools based on verbal pain descriptions can be used to help determine the presence of neuropathic pain. Several screening tools like the painDETECT, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) and Self-Administered Leeds Assessment of Neuropathic Symptoms and Signs (S-LANSS) have been developed for neuropathic pain screening.

The painDETECT was developed to detect neuropathic pain components in chronic low back pain patients, however it has been validated for use across musculoskeletal pain conditions.^(5, 7) The painDETECT has a sensitivity of 85%, specificity of 80% and positive predictive accuracy of 83%.⁽⁷⁾

The LANSS has shown sensitivity of 85% and specificity of 80% in detecting neuropathic pain.⁽²⁵⁾ The S-LANSS is a validated self-report version of the LANSS and has been shown to have sensitivity ranging from 74-78% and specificity ranging from 68-83% depending on cut-off score.⁽²⁶⁾ Positive scores on either questionnaire identify neuropathic pain mechanisms being present in the patient.

Management of Neuropathic Pain

For the purposes of this review, only pharmacological management of neuropathic pain will be discussed.

Based on our understanding of the pathophysiological processes in neuropathic pain, the general concept for treatment of neuropathic pain focuses on

- i. Reduction of peripheral sensitisation
- ii. Reduction of central sensitisation, and
- iii. Enhancement of the descending inhibitory pathways.

i. Reduction of peripheral sensitisation

- Sodium channel blockade
 - Tricyclic antidepressants (**Amitriptyline**, **Nortriptyline** and **Desipramine**) have several modes of action:
 - Inhibition of reuptake of serotonin and/or norepinephrine
 - Block sodium channels
 - Modulates mood

And have been shown to be effective in treating neuropathic pain conditions such as diabetic neuropathy, post herpetic

neuralgia, chronic radiculopathy and neuropathic pain post breast cancer treatment.⁽²⁷⁻³¹⁾

- **Lidocaine** (topical) works by blocking sodium channels and has been shown to be effective in the treatment of peripheral neuropathic pain syndromes.⁽³²⁾

ii. Reduction of central sensitisation

- NMDA antagonists (Ketamine, Methadone)
 - **Ketamine** is an NMDA receptor antagonist which works by inhibiting “the progressive increase in action potential discharge (wind-up) and neuronal hyperexcitability produced by repeated stimulation of small-diameter primary afferents.”⁽³³⁾ A small pilot study on the use of intraoperative ketamine during knee arthroplasty has indicated that when used in conjunction with spinal anaesthesia, it may be able to influence the reduction of persistent post total knee arthroplasty pain.⁽³⁴⁾ The normal route of ketamine administration is either via intravenous or subcutaneous infusions. However, an oral/sublingual route of administration has been developed with good results.⁽³⁵⁾
- Calcium channel blockers
 - **Pregabalin** and **Gabapentin** are calcium channel $\alpha 2\text{-}\delta$ ligands that reduce the release of excitatory neurotransmitters. Multiple studies have shown the effectiveness of both pregabalin and gabapentin in the management of neuropathic pain.⁽³⁶⁻⁴⁰⁾
 - **Pregabalin** has been shown to be effective for use in diabetic neuropathy, post herpetic neuralgia and central pain after spinal cord injury.⁽⁴¹⁾
 - **Gabapentin** has been shown to be effective for use in diabetic neuropathy, post herpetic neuralgia and cancer associated neuropathic pain.⁽⁴¹⁾

iii. Enhancement of the descending inhibitory pathways

- Tricyclic antidepressants (TCA), Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) and opioids all work to enhance the descending inhibitory pathways via inhibition of norepinephrine and serotonin reuptake.
- SNRI
 - **Duloxetine** is a Serotonin Norepinephrine Reuptake Inhibitor (SNRI), which works by inhibiting reuptake, thus increasing the levels of serotonin and norepinephrine in the CNS. Multiple studies have shown Duloxetine to be an effective pain relief for patients suffering from diabetic neuropathy.⁽⁴²⁻⁴⁵⁾
- Opioids
 - **Tramadol** is a centrally acting drug that has a μ -opioid effect and also inhibits norepinephrine and serotonin reuptake. It has been shown to be effective in the treatment of diabetic neuropathy and polyneuropathy.^(46, 47)
 - **Tapentadol** is a newer drug that has a μ -opioid receptor agonism effect and also inhibits noradrenaline reuptake.
 - Tapentadol has been shown to be more effective than morphine in the treatment of diabetic neuropathy in the animal model.⁽⁴⁸⁾ In a human trial, Tapentadol demonstrated a 30% improvement in pain intensity for 60.5% of research participants with diabetic neuropathy.⁽⁴⁹⁾
 - Tapentadol has demonstrated effectiveness in the treatment of chronic low back pain with/without neuropathic pain component⁽⁵⁰⁾, and also was associated with a lower incidence of adverse events as compared to oxycodone in the treatment of chronic low back pain.⁽⁵¹⁾

Combination therapy

Combination therapy in the treatment of neuropathic pain is promising. Typically, with combination therapy the individual doses of each drug is much lower as compared to single drug therapy.

A study which looked at combination of oxycodone with gabapentin found better results in patients with diabetic neuropathy as compared to mono therapy.⁽⁵²⁾ Combination of morphine with gabapentin,⁽⁵³⁾ nortriptyline and gabapentin,⁽⁵⁴⁾ and topical lidocaine with pregabalin,⁽⁵⁵⁾ also demonstrated better results than mono therapy in patients suffering from diabetic neuropathy and post herpetic neuralgia. Combination therapy of oxycodone and pregabalin was administered to patients diagnosed with neuropathic pain of various etiologies (due to either Lumbar stenosis, Failed Back Surgery Syndrome, Post herpetic neuralgia, Diabetic neuropathy or Radiculopathy), the group that received combination therapy fared significantly better compared to the mono therapy group.⁽⁵⁶⁾

Current Pharmacological Guidelines for the Treatment of Neuropathic Pain

The recommended first line pharmacological treatment of neuropathic pain are calcium channel blockers (gabapentin/pregabalin), TCA/SNRI or sodium channel blockers (topical lidocaine).^(41, 57, 58)

Conclusion

Neuropathic pain is complex and extremely challenging for healthcare professionals to handle. Due to the multiple mechanisms and the variability of these mechanisms, each individual with neuropathic pain is unique and different. Pharmacological management of the neuropathic pain patient must be targeted to their specific pain pathways. In addition, neuropathic pain sufferers also tend to be more depressed, have higher anxiety levels and disturbances to sleep, these factors all need to be addressed in their individual treatment plan.

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Chapter 4: Specialised Physiotherapy

Clinics

4.1 Introduction

In this unit, students undertake an advanced clinical placement intended to improve their knowledge and skills in a specialised area of clinical practice. The placement may involve advanced physiotherapy practice or extended scope practice in an area relevant to the personal development of the student. It is envisaged that supervision will be provided by a physiotherapist with specialist knowledge and skills or by a medical practitioner with specialist knowledge and skills.

The placement will be structured to provide specific learning opportunities for the student. This is a Doctoral level placement and will involve a high level of self-directed learning leading to the development of specific expertise. It is envisaged that the placement will involve evidence based practice and will include a specific emphasis on utilizing and understanding specific outcome measures as a means to evaluate practice.

The contact time for this unit was 96 hours.

4.2 Syllabus

- Supervised clinical practice with an emphasis on development of advanced competencies in a specific area of physiotherapy practice.
- Emphasis on advanced skills in patient/client communication, physical examination, interpretation of clinical information and development of evidence-based physiotherapy treatment plans.
- Evaluation of response to treatment and modification of treatment at an advanced level.
- Understanding of the indications for inter-professional patient/client referral and inter-professional management consistent with advanced practice in physiotherapy.

4.3 Learning Contract

PHTY7012 SPECIALISED PHYSIOTHERAPY CLINICS DOCTORAL PLACEMENT LEARNING CONTRACT FORM

Supervisor's Name: Prof. Stephan A Schug

Position: Chair of Anaesthesiology
Pharmacology, Pharmacy and Anaesthesiology Unit
School of Medicine and Pharmacology
University of Western Australia

Director of Pain Medicine
Royal Perth Hospital

Address: UWA Anaesthesiology
Level 2 MRF Building
Royal Perth Hospital
GPO Box X2213
Perth, WA 6847

Student's Name: Philip Cheong

Placement Title: Pain Medicine

Placement Dates: 15/03/16, 17/03/16, 21/03/16 to 01/04/16, 05/04/16,
07/04/16 and 11/04/16

Placement Goals and Objectives:

- (1) Develop an increased understanding of the roles of each of the multidisciplinary team members in the Pain Medicine clinic by the end of the placement
- (2) Develop understanding of different types of pain syndromes seen at the Pain Medicine clinic
- (3) Acquire knowledge on the procedures/interventions used by the Pain Medicine physicians on patients with acute and chronic pain
- (4) Identify areas where physiotherapy can play a part in the management of pain disorders
- (5) Help with the administration of LEAP (Lifestyle Education & Activation Program) for chronic pain sufferers

Proposed Outcome Measures:

- (1) Develop a standardised assessment form for LEAP which includes questionnaires and a functional outcome measure

I/we agree to provide a placement, which will meet the above stated objectives for Philip Cheong for the time frame stated under project dates. I acknowledge that this placement is approved by the School of Physiotherapy and Exercise Science at Curtin University. I agree to participate fully in the evaluation of this placement.

Supervisor Signature:


Date:

11/4/16

I agree to undertake a placement, which meets the above stated objectives for this facility for the time frame stated under placement dates.

Student Signature:  Date: 11/3/16

4.4 Supervisor Evaluation Form

 Curtin University	Supervisor Evaluation Form
School of Physiotherapy & Exercise Science	Physiotherapy Clinics 754

Supervisor's Name: Professor Stephan Schug

Position: (1) Chair of Anaesthesiology – Pharmacology, Pharmacy and Anaesthesiology Unit,
School of Medicine and Pharmacology, UWA
(2) Director of Pain Medicine, Royal Perth Hospital

Address: UWA Anaesthesiology, Level 2 MRF Building, Royal Perth Hospital,
GPO Box X2213, Perth, WA 6847

Student's Name: Phillip Cheong

Placement Area: Pain Medicine

Placement Dates: 15/03/16, 17/03/16, 21/03/16 to 01/04/16, 05/04/16, 07/04/16 and 11/04/16

Supervisor to complete this section

	The student:	Agree	Disagree	N/A
1	demonstrated a high level of communication skills	<input checked="" type="checkbox"/>		
2	liaised appropriately with the supervisor and other staff during the placement	<input checked="" type="checkbox"/>		
3	displayed a high degree of clinical competence during the placement	<input checked="" type="checkbox"/>		
4	made a valuable contribution to the organisation during their placement	<input checked="" type="checkbox"/>		
5	achieved the majority of placement objectives	<input checked="" type="checkbox"/>		

Please indicate any aspects of the placement objectives that were not achieved and give brief reasons for this.

None

Was the student's presentation to staff of a satisfactory standard?

☒ Yes ☐ No

Comments:

More than satisfactory.
Very highly regarded by all members of team

Please provide any suggestions that you might have for ways in which the student could improve their clinical expertise:

None



In your opinion, was the overall performance of this student:

Not adequate ☐

Adequate ☐

Good ☐

Excellent ☒

In relation to advanced clinical practice.

Additional comments:

It was a pleasure to have
this student attached to our
service

Supervisor Signature: _____

Date: _____

11/4/16

Please return to: Prof Tony Wright, School of Physiotherapy, Curtin University, GPO Box U1987 Perth WA 6845



4.5 Overview of Placement

Pain Medicine is recognized as a medical specialty that uses a multidisciplinary approach in the reduction/management of pain and improving quality of life. The areas of pain medicine include acute pain, chronic pain and cancer pain.

At Royal Perth Hospital, Pain Medicine is divided into 2 branches: Acute Pain Service (APS) and Pain clinic (dealing with chronic pain issues).

Acute Pain Service

The role of the APS is to:

- Provide/improve post-operative analgesia
- Conduct daily rounds to ensure that all post-operative patients have adequate pain relief
- Educate ward staff in the current clinical guidelines in acute pain management

The APS team members include Pain Medicine Specialists, Nurse Practitioners and Clinical Nurses.

Pain Clinic

The role of the pain clinic is to:

- Provide a multidisciplinary approach to the diagnosis and management of chronic pain conditions in an outpatient setting
- Tailor a management plan to each patient's specific needs

The Pain Clinic team members include Pain Medicine Specialists, Nurse Practitioners, Clinical Nurses, Psychiatrist, Clinical Psychologists and Physiotherapists.

During the placement at RPH Pain Medicine, I had the unique opportunity to experience and take part in all aspects of pain medicine.

4.6 Placement Goals and Objectives

1. Develop an increased understanding of the roles of each of the multidisciplinary team members in the Pain Medicine clinic by the end of the placement
 - a. Pain Medicine Specialist
 - i. Observed and participated in clinic sessions with various Pain Medicine Consultants
 - ii. Gained knowledge on the pharmacological and interventional approaches for chronic pain
 - b. Nursing
 - i. Observed and participated in patient education sessions on chronic pain management
 - ii. Observed the scope of nursing practice in pre and post procedures/interventions
 - c. Psychiatry
 - i. Was not able to observe due to patient confidentiality issues
 - d. Clinical Psychology
 - i. Observed an initial assessment session, but not able to join in during treatment sessions due to patient confidentiality issues
 - ii. Gained knowledge on the use of different psychological approaches (Cognitive Behavioral Therapy (CBT) and Acceptance & Commitment Therapy (ACT))
 - e. Physiotherapy
 - i. Observed and participated in triage clinic sessions with the extended scope physiotherapist
 - ii. Participated in joint clinic sessions with the Pain Medicine Consultants

2. Develop understanding of different types of pain syndromes seen at the Pain Medicine clinic
 - a. Developed deeper understanding in the presentation and management of the following conditions:
 - i. Fibromyalgia
 - ii. Osteoarthritis
 - iii. Phantom Limb Pain
 - iv. Non-specific Chronic Low Back Pain
 - v. Cervicogenic Headaches
 - vi. Neck Pain
3. Acquire knowledge on the procedures/interventions used by the Pain Medicine physicians on patients with acute and chronic pain
 - a. Acute Pain
 - i. Developed deeper understanding on the different medications (and mode of administration) used on the Analgesic Ladder.
 - ii. Learnt about the following analgesic infusions and their uses
 1. Patient Controlled Analgesia
 2. Opioid Infusion
 3. Epidural Infusion
 4. Regional Infusion
 5. Ketamine Intravenous Infusion
 - b. Chronic Pain
 - i. Observed the following procedures and developed deeper understanding of the purpose of the procedure and the structures affected
 1. Medial Branch Block
 2. Lateral Femoral Cutaneous Nerve Block
 - ii. Due to funding cuts, the number of interventional procedures has dropped significantly. Therefore I was only able to observe 2 interventions.

4. Identify areas where physiotherapy can play a part in the management of pain disorders
 - a. Physiotherapists can play a number of roles in the spectrum of pain management
 - i. Triage clinics
 1. No specific additional training is needed, as the role of the triage clinic is to determine which health professional that the patient needs to be seen by.
 - ii. Extended/Advanced scope practice
 1. Specific training needed on
 - a. Pharmacology
 - b. Training program on management of pain disorders
 - c. Psychological approaches (CBT and ACT)
 2. With the additional training, physiotherapists can offer medication counseling and simple psychological intervention
5. Help with the administration of LEAP (Lifestyle Education & Activation Program) for chronic pain sufferers
 - a. Multidisciplinary pain management program that incorporates pain medicine, clinical psychology, occupational therapy, physiotherapy and dietitian input.
 - b. Observed and participated in the administration of the LEAP program
 - i. Assisted in the physiotherapy-led exercise classes

4.7 Outcome Measure

A standardised assessment form for LEAP was developed and implemented for use for assessment of future LEAP participants. Refer to Appendix 1 for assessment form.

Functional Outcome Measure

1. The Aggregated Locomotor Function Score (ALF) has been incorporated as the functional outcome measure for the assessment form. The ALF is a measure of observed locomotor function. It consists of 3 components: 8 metres walk time, stair ascent and descent time and transferring time⁽¹⁾.

The ALF has been shown to have excellent intra-tester reliability ($ICC_{2,k}$: 0.99; 95% CI: 0.98-0.99), low standard error of measurement (0.86 s) and smallest detectable difference (9.5%) values⁽¹⁾. The ALF was chosen as it featured 3 functional movements that all LEAP participants experience in their daily activities.

Questionnaires

1. The Pain Catastrophising Scale (PCS) is a self-report questionnaire describing thoughts and feelings that individuals might experience when in pain. It has 13 items over 3 subscales: rumination, magnification and helplessness⁽²⁾. The PCS demonstrated adequate reliability (Cronbach's Alpha: 0.87)⁽²⁾; (Cronbach's Alpha: 0.91 for rumination subscale; 0.75 for magnification subscale; 0.87 for helplessness subscale; 0.93 for total PCS)⁽³⁾, and good criterion-related, concurrent and discriminant validity⁽⁴⁾.
2. The Tampa Scale of Kinesiophobia (TSK) assesses fear of movement/physical activity and/or (re)injury in individuals with pain^(5, 6). The TSK demonstrates adequate reliability (Cronbach's Alpha: 0.77)⁽⁵⁾.

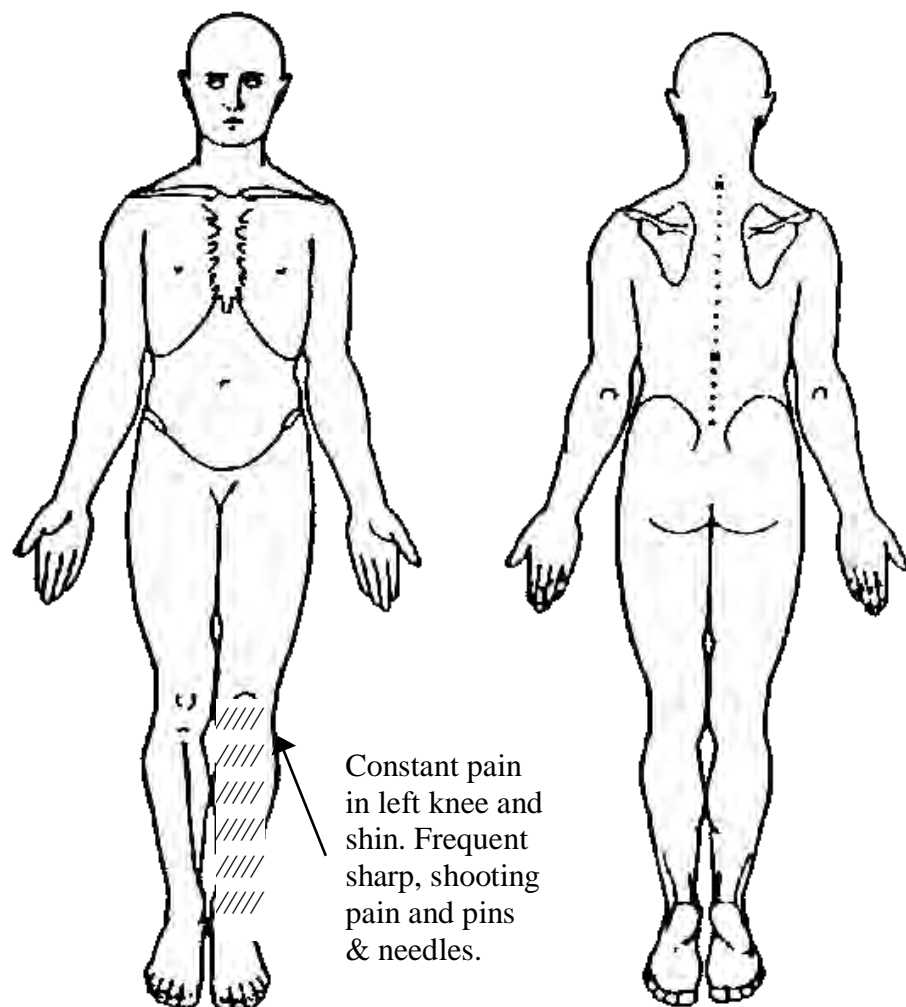
4.8 Case Studies

4.8.1 Case Study 1

Current History:

B.N. is a 65 year-old male who was diagnosed as having severe osteoarthritis (OA) of both knees in 2010. He states that he was coping well with his condition until 2 years ago, when he started to feel that the pain in his left knee started to worsen. He states that his pain has started to worsen even more over the last 6 months. He complains of pain from his left knee going down to his shin (refer to body chart). He states that he can walk a short distance (approximately 200 metres) but he prefers not to use his knees too much as he does not want to “wear them out further”. He has a BMI of 35. B.N. was screened and cleared of any red flags.

Body Chart:



Pain History:

B.N. reports that he is in constant pain. 2 years ago before the pain worsened, he stated that his pain was 4/10 on average then. Since 6 months ago, his pain is 12/10 on average. He states that pain shoots down from the left knee to the shin, and he often feels pins and needles and an electrical shooting pain in the same area. His pain worsens when the weather is hot. He is unable to wear jeans as the weight of the jeans resting/rubbing on his right knee and shin gives him pain. He is unable to work due to his pain (he used to work as a sheep shearer). His functional limitations are squatting (unable to do at all), climbing up and down stairs (only able to go up 2-3 steps), walking for 200 metres. He also reports that he is often unable to sleep for more than 2 to 3 hours at a time due to the pain. He complains of stiffness in both his knees (particularly in the morning that lasts about 10-15 minutes, and after sustained sitting).

Social History:

B.N. is a heavy smoker and averages about 20 cigarettes daily; he also drinks about 4 cans of beer daily. He lives on a sheep station, which is about a 4 hour drive on unpaved roads from the Kalgoorlie, with his wife. B.N. states that he has put on about 30 kg over the last 2 years. He states that this is due to the lack of physical activity (because of fear of further damage to his knees) and also his eating habits (frequent snacking of sweets and having big meals everyday). His wife was diagnosed with breast cancer 4 years ago, she received treatment and the cancer went into remission. However, during a follow up screening 3 months ago, the oncologist discovered that the cancer has relapsed and spread into her lymph nodes.

Medication:

B.N. is currently on Celecoxib (100mg, once daily) and Panadol Osteo (2 caplets, thrice daily). He has been on these medications and dosage for the last 2 years.

Investigations:

Radiographs of both knees show severe joint space narrowing and presence of multiple osteophytes.

Screening Tools and Outcome Measures:

The Western Ontario and McMaster Universities Arthritis Index (WOMAC), PainDETECT, Pain Catastrophizing Scale (PCS), Tampa Scale for Kinesiophobia (TSK) and Depression Anxiety Stress Scales (DASS 21) questionnaires were administered.

B.N. scored 73/96 for the WOMAC (Pain: 14/20, Stiffness: 5/8, Function: 54/68); this indicates that he has significant issues with pain, stiffness and performing daily activities.

B.N. scored 31/38 for the PainDETECT questionnaire. Due to the high score on the PainDETECT, it is likely that a neuropathic pain component is present. A score of >19 indicate that a neuropathic pain component is likely.

He scored 45/52 for the PCS (Rumination: 15/16, Magnification: 10/12, Helplessness: 20/24); this indicates that he demonstrates catastrophic thinking, which plays a role in heightening his pain intensity and magnification of his pain. A score of 30 represents a clinically relevant level of catastrophizing.

B.N. scored 65/68 for the TSK; this means that he has a high degree of kinesiophobia (irrational fear of movement due to vulnerability of re/injury). A score of 37 differentiates between high and low scores of kinesiophobia. For the DASS 21 questionnaire, his scores were: 28 (Depression Score); 14 (Anxiety Score); 34 (Stress Score). Based on the DASS 21 scores, B.N. has extremely severe depression scores, moderate anxiety scores and extremely severe stress scores.

Pain Management:

B.N. is currently only under the care of the general practitioner (GP) in Kalgoorlie, which he sees infrequently.

Patient Perspective:

B.N. expressed anger, anxiety and feeling very stressed over several issues (e.g. Loss of financial stability due to unemployment, severity of pain in his knee, wife's cancer relapse). He would like to be able to get back to doing some physical work around the house, however he tries not to move around much as he is worried about causing more damage to his knees. His GP has mentioned that a total knee replacement (TKR) might be a good solution for his knee pain, but he is not keen as he has a few friends that have had bad experiences after having had a TKR (worse pain after TKR, infection and no change in pain). He states that the only activity that he finds enjoyable now is eating. He feels like there is no joy in life anymore, and the thought of losing his wife is too much to bear. B.N. also mentioned that he has access to firearms and plenty of rope at home and he has thought that there is no point in living at times.

Physical Examination Findings:

- Knee Flexion:
 - Right: 120 degrees, P1 R2, 6/10 pain.
 - Left: 80 degrees, P2, 12/10 pain.
- Functional:
 - Squat: $\frac{1}{4}$ squat, 12/10 pain. Unable to squat lower.
 - Stairs: Up – Leads with right leg, and moves up step one at a time. Able to go up a maximum of 3 steps before needing to rest due to 12/10 pain. Down – Leads with left leg, and moves down step one at a time. Able to go down a maximum of 3 steps before needing to rest due to 12/10 pain.
 - Sit to stand = Uses arms to push up when standing. No eccentric control of knees when sitting down. Drops straight into chair when sitting.
- Sensory testing:

- Light touch with brush = 8/10 pain reproduced at left knee and shin.
- Light pressure = 7/10 pain reproduced at multiple sites (bilateral thighs, knees and shins).
- Cold (using test tube filled with ice water) = 7/10 pain reproduced at left knee and shin.
- Heat (using test tube filled with warm water) = 7/10 pain reproduced at left knee and shin.

Summary:

It is clearly evident that B.N. has both nociceptive and neuropathic pain, as well as features of peripheral and central sensitization. This is compounded by psychological factors (kinesiophobia, catastrophic thinking, and high DASS 21 scores - extremely severe depression scores, moderate anxiety scores and extremely severe stress scores) and his passive pain coping mechanisms.

Case Interpretation

OA Background

OA pain is complex; nociceptive, neuroplastic and neuropathic pain mechanisms, in combination with psychological and social factors (e.g. pain catastrophising, depression, anxiety, lack of social support, lower socioeconomic status) have been shown to contribute to the generation of OA pain⁽⁷⁾. The presentation of pain in knee osteoarthritis sufferers varies greatly, from localised activity-related pain to referred or even widespread pain at sites distant from the knee⁽⁷⁻¹⁰⁾.

There are multiple mechanisms (nociceptive pain, neuroplastic pain and neuropathic pain), pain processes (peripheral sensitization, central sensitization), and psychological/social factors that contribute to the generation of OA pain^(7, 11). To further complicate the nature of OA pain; the mechanisms, pain processes and factors that mediate OA pain vary among individuals^(7, 11).

Current Neurobiology Pain Perspective:

Based on the clinical findings, B.N's pain profile comprises of nociceptive, inflammatory and neuropathic pain

The evidence that supports the presence of nociceptive pain are:

- Knee range-of-motion
- Functional tasks (limitations)

The evidence that supports the presence of inflammatory pain are:

- Morning stiffness in knees
- Allodynia in affected area (as evidenced by light touch with brush)
- Mechanical hyperalgesia in affected area (as evidenced by light pressure)

The evidence that supports the presence of neuropathic pain are:

- High PainDETECT questionnaire score (31/38)
- Shooting pain from left knee to shin
- Pins and needles and numbness in the affected area
- Pain in the affected area if the weather is hot
- Weight of jeans on his left knee gives him pain
- Cold/Heat hyperalgesia in affected area
- Allodynia in affected area
- Mechanical hyperalgesia in affected area

B.N. also appears to have features of peripheral sensitization (localised pain and sensitivity) and central sensitization (widespread sensitivity to light pressure and cold). Injury and inflammation results in profound changes in the chemical milieu of the nociceptors. This leads to increased responsiveness and reduced threshold of nociceptors to stimulation of their receptive fields. Post-translational processing (phosphorylation) and altered gene expression are the main mechanisms of peripheral sensitisation⁽¹²⁾. Spontaneous ectopic activity and the constant barrage of nociceptive input from the osteoarthritic knee most likely initiated the central sensitization^(12, 13).

His pain is also compounded by the presence of psychological distress (i.e. depression, anxiety, stress) and his belief systems (i.e. passive pain management mentality, kinesiophobia, pain catastrophising). Stress causes the hypothalamus to secrete CRH, which stimulates the pituitary to secrete ACTH, which then stimulates the synthesis of cortisol. Simultaneously, the adrenal glands are stimulated and secrete adrenalin. Uncontrolled stress leads to the impaired regulation of the immune and stress systems which have been found to have links between mood disorders and inflammatory disease⁽¹⁴⁾. Catastrophising, anxiety, fear of movement and individual's experiences and belief systems can act to increase the perception of OA pain⁽¹⁵⁾.

Current Clinical Guidelines:

Based on the current guidelines for conservative management of patients with knee OA⁽¹⁶⁾, there are a number of gaps in the management of B.N.'s condition. The gaps that need to be addressed are:

1. Education of his condition
 - a. He was never educated on his condition and has no clear understanding of the pathophysiology of OA and the current clinical best practice guidelines on the treatment of OA.
 - b. There is a pressing need to change his current belief system on the management of his condition, this will help to change his passive approach to pain management to a more active one.
2. Prescription of an appropriate exercise program
 - a. The success of an appropriate exercise program for him will depend on his understanding of his condition, as well as changing his belief system to be in line with an active pain management approach.
 - b. Low impact exercises and strength training will make up the basis of his exercise program.
3. Weight management plan

- a. His BMI is 35, which puts him in the obese range. As per current best practice guidelines⁽¹⁶⁾, reduction in weight has been shown to reduce pain levels.
- 4. Pharmacological management plan
 - a. He is currently on Celecoxib (100mg, once daily) and Panadol Osteo (2 caplets, thrice daily). But his pain levels are still not well controlled. Current guidelines⁽¹⁶⁾ recommend the use of NSAIDs as being appropriate for chronic knee OA pain. Use of tramadol is not suitable, as there is a precaution for use of tramadol on individuals that have a suicide risk. Furthermore, if he is diagnosed as being clinically depressed, tramadol has a precaution for use for individuals that are on TCAs and SSNRIs. Tapentadol has been shown to be effective for the management of mixed pain (nociceptive and neuropathic), hence it might be a suitable analgesic for B.N.
 - b. It is important that he is treated pharmacologically for the neuropathic pain. Current evidence⁽¹³⁾ recommends treating neuropathic pain with low dose TCAs, SSNRIs, calcium channel $\alpha 2$ - δ ligands, topical lidocaine or opioid agonists. The use of TCAs and SSNRIs for the treatment of his neuropathic pain might not be suitable, pending his diagnosis of depression and pharmacological treatment. The most logical pharmacological treatment for B.N.'s neuropathic pain is to start a course of pregabalin. A benefit of pregabalin is the improvement of sleep disturbances and reduction in anxiety.

Treatment:

- 1. Education of condition
 - a. Educated B.N. on OA
 - b. Explained that pain does not necessarily equate to damage or harm.

- c. Encouraged normal movement.
- d. Resources on OA from WA Arthritis Foundation given to B.N.

2. Exercise program

- a. Reinforced that normal movement is the first step to getting better.
- b. Stationary bicycle (he has access to a stationary bicycle at home that his wife uses for exercise)
 - i. Start with minimal resistance, 5 minutes, thrice daily, for the first 2-3 weeks.
 - ii. To increase duration by 3 minutes every week after the third week.
- c. Strengthening exercises, 3 times daily
 - i. Straight leg raise
 - 1. 3 sets of 5 repetitions with 5 seconds hold
 - ii. Bridging
 - 1. 3 sets of 5 repetitions with 5 seconds hold
 - iii. Sit to stand
 - 1. Start with 1 set of 5 repetitions
 - 2. No use of arm rests allowed
 - 3. To control descend from standing to sitting
 - 4. Progress to 3 sets of 5 repetitions in 8 weeks time

3. Weight management plan

- a. Reviewed current diet
 - i. Substitute consumption of soft drinks and sweets with fresh fruits
 - ii. Referral to dietitian
- b. Increase daily activity via exercise program

4. Medications

- a. Referral to pain medicine physician
- b. Wrote a note to his GP to review B.N.'s pain medications
 - i. Recommendations

1. Increase Celecoxib to 100mg, twice daily
 2. Start Pregabalin 75mg, twice daily. Titrate as needed
 3. Explore use of Tapentadol.
5. Interdisciplinary referrals
- a. Psychiatrist (Urgent referral)
 - i. To assess his psychological distress and suicide ideation
 - b. GP/Pain management doctor
 - i. To review, recommend and titrate medications that will suit his condition.
 - c. Clinical psychologist
 - i. To change current belief system
 - ii. Teach coping strategies
 - iii. Help organize a better sleep pattern
 - d. Dietitian
 - i. Review and set a nutrition plan for weight control

Learning achieved

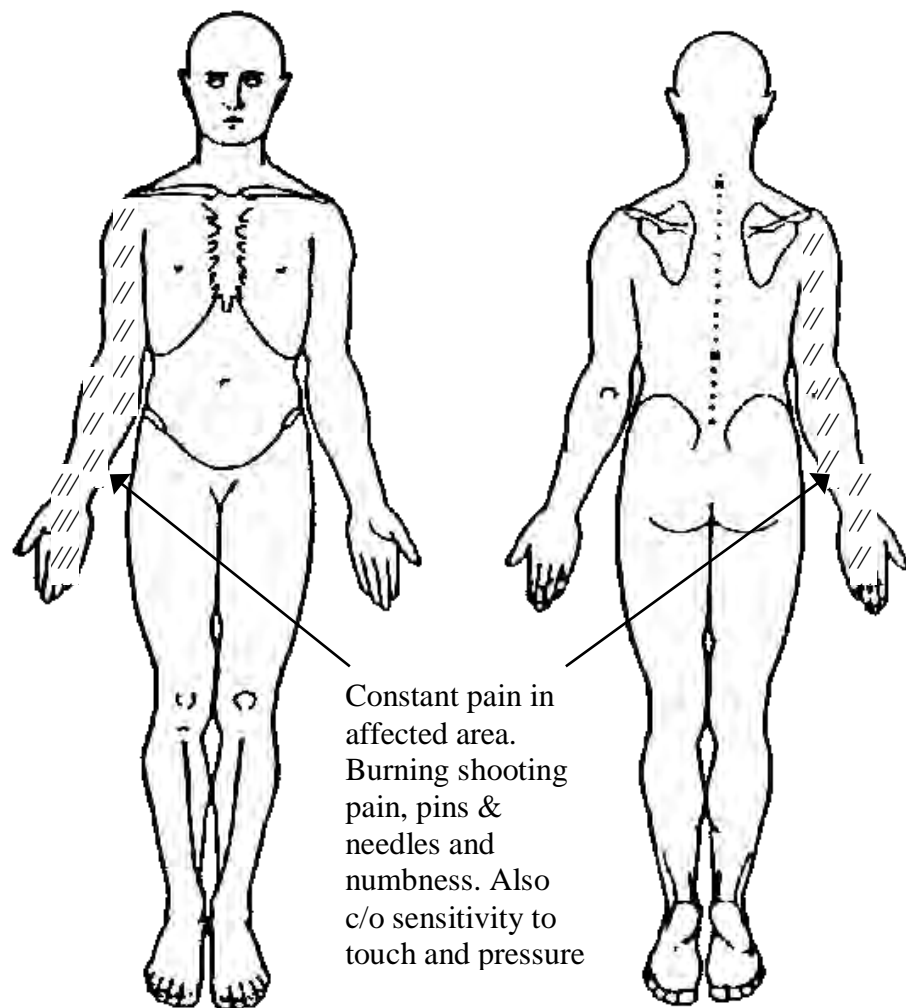
1. Chronic pain is multi-dimensional and it is important to integrate its different aspects (physical presentation, physiological and psychological) in order to ensure that the patient is managed appropriately.
2. Knowing when to appropriately refer out to other health care professionals is critical.
3. Clear communication is very important
 - a. To patient
 - b. To other health care professionals

4.8.2 Case Study 2

Current History:

C.J. is a 30 year-old male who was diagnosed as having post-herpetic neuralgia (PHN) (affecting the right arm – C5/6, C6/7 and C7/8 dermatomes) in November 2015. C.J. has a classical case of PHN as his symptoms appeared a year after he had recovered from right-sided shingles. He has a BMI of 30, and he has been screened and cleared of any red flags. Other than his weight, C.J. does not have any medical conditions.

Body Chart:



Pain History:

C.J. reports that he has constant pain and sensitivity in his right arm. He rates that pain as 5/10 on average, but whenever it flares up, it can go up to 10/10. Flare-ups can be caused by changes in temperature (weather, hot/cold shower) and if he uses his arms excessively. He is unable to wear any type of long sleeved clothing as the rubbing of the clothing on his right arm increases his pain. However, he states that having a compression bandage over the right arm helps to keep his pain manageable. The compression bandage is kept on most of the time. He only takes it off when he needs to shower. He was previously working in retail, but is currently unemployed due to his condition. His functional limitations are lifting/carrying anything more than 2kg.

Social History:

C.J. does not smoke and only drinks alcohol occasionally. He is currently staying in shared accommodation. He has been unemployed since January 2016, and spends most of his time at home. He will go over to his grandmother's place once a week to help her out with some simple maintenance tasks. He used to exercise regularly (walking for 1 hour 4-5 times weekly), but has stopped ever since he started getting the pain in his right arm. Due to the cessation of his walks and his unemployment, he has put on about 5-10 kgs over the last few months. C.J. furthered revealed that he really enjoyed his walking, but his pain got too unbearable after doing half the distance of his normal walks.

Medication:

C.J. is currently on Pregabalin (75mg, twice daily), Amitriptyline (10mg, nocte) and Tramadol (50mg, up to four times daily). He has been on these medications and dosage since November 2015.

Screening Tools and Outcome Measures:

The Brief Pain Inventory (BPI) Short form, Pain Catastrophizing Scale (PCS), Tampa Scale for Kinesiophobia (TSK) and Depression Anxiety Stress Scales (DASS 21) questionnaires were administered.

For the BPI, C.J. scored 8/10 for the Pain Severity Score and 5/10 for the Pain Interference Score. (Note: he scored 5/10 for interference with walking ability)

C.J. scored 33/38 for the PainDETECT questionnaire. Due to the high score on the PainDETECT, it is likely that a neuropathic pain component is present. A score of >19 indicate that a neuropathic pain component is likely.

He scored 11/52 for the PCS (Rumination: 2/16, Magnification: 3/12, Helplessness: 6/24); this indicates that he does not catastrophise. A score of 30 represents a clinically relevant level of catastrophizing.

B.N. scored 26/68 for the TSK; this means that he has a low degree of kinesiophobia. A score of 37 differentiates between high and low scores of kinesiophobia.

For the DASS 21 questionnaire, his scores were: 10 (Depression Score); 12 (Anxiety Score); 19 (Stress Score). Based on the DASS 21 scores, he has mild depression scores, moderate anxiety scores and moderate stress scores.

Pain Management:

C.J. is currently under the care of his general practitioner (GP) in Booragoon. He just had a review with the GP a fortnight ago.

Patient Perspective:

He has expressed frustration at the pain levels and his inability to hold on to a job due to his pain. He would like to find some part-time work once he is able to gain some control over his pain levels. He is trying to remain active but is hesitant to start with his walking routine, as he does not want to aggravate his condition.

Physical Examination Findings:

- Upper limb AROM:
 - FROM with shoulders, elbows and wrists.
 - Pain levels in right arm remained stable at 5-6/10.
- Sensory testing:
 - Light touch with brush = 10/10 pain reproduced at right C5/6, C6/7 and C/78 dermatomes.
 - Light pressure = 10/10 pain reproduced at right C5/6, C6/7 and C/78 dermatomes.
 - Cold (using test tube filled with ice water) = 10/10 pain reproduced at right C5/6, C6/7 and C/78 dermatomes.
 - Heat (using test tube filled with warm water) = 8/10 pain reproduced at right C5/6, C6/7 and C/78 dermatomes.

Summary:

It is clear that C.J. has neuropathic pain. He has fairly low levels of psychological distressed as evidenced by the questionnaires. However, the levels of psychological distress have a high chance of increasing, if his pain levels are not brought under better control.

Case Interpretation

PHN Background

PHN is the most common complication that comes on after an episode of herpes zoster⁽¹⁷⁾. The exact pathophysiological mechanisms of PHN pain are poorly understood. PHN may be caused by the damage to the primary afferent neuron or dorsal root ganglion during the initial acute episode of herpes zoster; this can lead to sensitisation of these structures that lead to spontaneous activity causing pain^(17, 18). Peripheral and central mechanisms have been shown to have a likely role in the maintenance of PHN pain^(18, 19).

Current Neurobiology Pain Perspective:

Based on the clinical findings, C.J.'s pain profile comprises mainly of neuropathic pain

The evidence that supports the presence of neuropathic pain are:

- High PainDETECT questionnaire score (33/38)
- Burning, shooting pain in the affected area
- Pins and needles and numbness in the affected area
- Cold/Heat hyperalgesia in affected area
- Allodynia in affected area
- Mechanical hyperalgesia in affected area

Current Clinical Guidelines:

Based on the current guidelines for conservative management of patients with PHN, treatment is based on symptom control^(20, 21).

1. Psychological interventions
 - a. PHN has been shown to have adverse affects on quality of life, and psychological interventions need to be given if indicated^(17, 22).
 - b. However, C.J. shows minimal levels of psychological distress, therefore psychological intervention is not needed at this time.
2. Pharmacological management plan
 - a. He is currently on Pregabalin (75mg, twice daily), Amitriptyline (10mg, nocte) and Tramadol (50mg, up to four times daily).
 - b. Current evidence^(13, 20, 21) recommends treating PHN pain with low dose TCAs, calcium channel $\alpha 2$ - δ ligands, topical treatments (lidocaine patch, capsaicin cream or patch) and opioids.

Treatment:

1. Education

- a. C.J. has good knowledge and understanding of his condition. Hence, no further education on his condition is warranted.
- b. Educated on the need to remain physically active to get good outcome

2. Exercise program

- a. Exercise is not in the list of recommended treatments in the clinical guidelines for PHN. However, exercise has been frequently cited as a key factor in the management of chronic pain. Hence an exercise program was prescribed to C.J.
- b. Walking
 - i. Start with 15 minute walks, three times a week.
 - ii. To increase duration by 5 minutes every week after the third week.
- c. Strengthening exercises (with a 500ml water bottle), 3 times daily
 - i. Shoulder flexion
 - 1. 3 sets of 10 repetitions
 - ii. Shoulder abduction
 - 1. 3 sets of 10 repetitions
 - iii. Bicep curls
 - 1. 3 sets of 10 repetitions

3. Desensitization protocol

- a. Advised C.J. to take off compression bandage as often as possible
- b. To lightly stroke his right arm with a cotton swab at least 3 to 5 times a day

4. Weight management plan

- a. Increase daily activity via exercise program

5. Medications

a. C.J. was seen in a joint consultation with the pain medicine consultant; hence the pain medicine consultant adjusted the medication as below.

1. Increased Pregabalin to 150mg, twice daily.
2. Increase Amitriptyline to 25mg, nocte.
3. Discontinued Tramadol.
4. Started Tapentadol 100mg, twice daily.

Learning achieved

1. Titration of medication is essential to ensure that the patient has adequate pain cover. In this case, the choice of medications prescribed to the patient by his GP is mostly correct. However, the level of each medication is too low to be of effective use.

4.9 Problems with the placement

There were no problems/issues faced during the placement. However, sourcing for a suitable placement proved to be a major difficulty for myself as I have not worked in Australia for a number of years and hence did not have the contacts needed to acquire and confirm a placement until 2016. The change in funding model for public healthcare provision in Western Australia also proved to be a big hurdle for me to secure a placement. Previous arrangements to secure a clinical placement in Pain Medicine at Sir Charles Gairdner Hospital fell through due to the funding cuts.

4.10 Changes that could have improved the original placement plan

I feel that no changes are needed. I would have preferred to have more time at the placement, 96 hours is considerably short for an advanced level placement.

4.11 Contribution of placement to professional and personal development

I have derived a considerable sum of benefit from this placement. The knowledge gained from this placement has increased my understanding of pain and its management.

4.12 Conclusion

This placement has been immensely beneficial to my learning and continuing development. Physiotherapists deal with pain everyday and it is pertinent that we are familiar with all aspects of pain management in order for us to provide proper care for our patients. Higher emphasis on pain education (which should include physiology of pain, pain pharmacology and pain psychology units) is needed at both undergraduate and postgraduate physiotherapy degree courses.

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Appendix 1 (LEAP Assessment Form)



Royal Perth Hospital

LEAP Assessment Form

DATE: _____

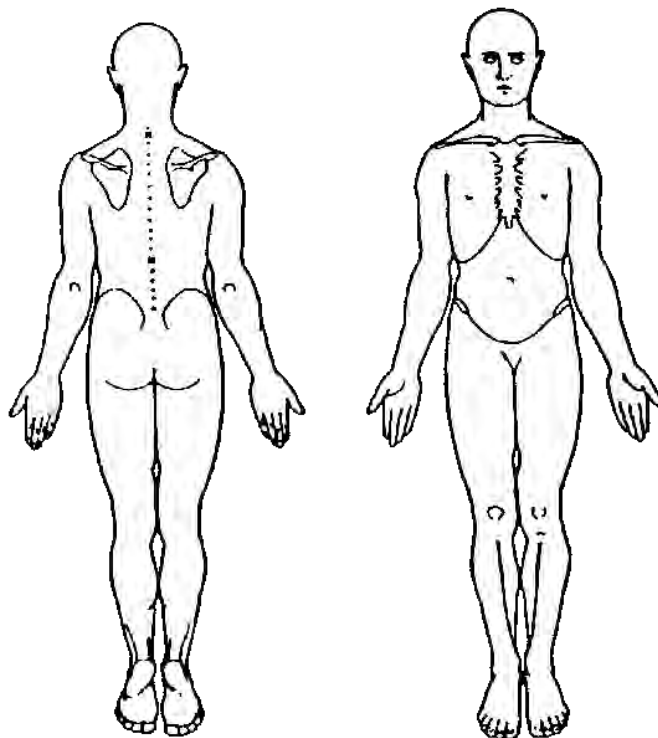
Height: _____

Weight: _____

BMI: _____

Subjective Hx

Mark painful areas



Pain Levels

At Best:

At Worst:

<u>Co-Morbidities</u>	<u>Current Medications</u>

<u>Previous Rx</u>	<u>Attendance Hx (Last 5 sessions)</u>
<u>Objective Examination</u>	
<u>Aggravating Activities and Pain Levels</u>	
(1)	
(2)	
(3)	

<u>ALF</u>		
<u>8 metre walk</u>	<u>Stairs ascent and descent</u>	<u>Transfer</u>
<u>Walking aid</u>	<u>Alternate legs</u>	
	<u>Always lead with 1 leg</u>	
	<u>Used railings</u>	

<u>Objectives of LEAP explained to patient</u> <div>YES</div> <div>NO</div>	<u>Patient agreeable to take part in LEAP</u> <div>YES</div> <div>NO</div>
<u>Is patient suitable for LEAP?</u> <div>YES</div> <div>NO</div>	TSK Scores: PCS Scores:
<u>If not suitable, please explain why and state further management plan</u> 	

Physiotherapist: _____
Signature: _____